CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206829sOrig1s008

Trade Name:	**Zerbaxa, Injection and Intravenous Use**
Generic or Proper Name:	(Ceftolozane and Tazobactum)
Sponsor:	**Cubist Pharms LLC**
Approval Date:	June 03, 2019
Indication:	Zerbaxa is indicated for the treatment of patients 18 years and older with complicated intra-abdominal infections (clAl) caused by the following susceptible Gram-negative and Gram-positive microorganisms: *Entrobacter cloacae, Escherichia coli, Klebsiella oxyoca, Klebsiella pneumonia, Proteus mirabilis, Pseudoonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.*

CENTER FOR DRUG EVALUATION AND RESEARCH

206829sOrigs1008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 206829/S-008

SUPPLEMENT APPROVAL

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Lillian Ting, PhD
Director, Global Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY 34-B188
Rahway, NJ 07065-0900

Dear Dr. Ting:

Please refer to your supplemental new drug application (sNDA) dated December 3, 2018, received December 3, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZERBAXA (ceftolozane and tazobactam) injection, for intravenous use.

This Prior Approval supplemental new drug application provides for a new indication, for the treatment of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia (HABP/VABP).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENT

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of the final report for the clinical study in HABP/VABP in children from birth to less than 18 years of age until November 2023.

Your deferred pediatric study is a required postmarketing study (PMR) under section 505B(a) of the Federal Food, Drug, and Cosmetic Act. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3637-1	Conduct a safety and pharmacokinetic study in HABP/VABP in children from birth to less than 18 years of age.	
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	04/2023
	Final Report Submission:	11/2023

Future submissions to the IND regarding this PMR should include a cross-reference letter to this NDA.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The report of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the report, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENT**" in large font, bolded type at the beginning of the cover letter of the submission.

We remind you that there are postmarketing requirements listed in the December 19, 2014, NDA approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

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[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Deborah Wang, PharmD, Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
    - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
06/03/2019 01:35:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829sOrigs1008

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZERBAXA safely and effectively. See full prescribing information for ZERBAXA.

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage	
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1.3)	6/2019
Dosage and Administration (2)	6/2019

----------INDICATIONS AND USAGE----------

ZERBAXA (ceftolozane and tazobactam) is a combination of ceftolozane, a cephalosporin antibacterial, and tazobactam, a beta-lactamase inhibitor, indicated in patients 18 years or older for the treatment of the following infections caused by designated suscept ble microorganisms:

- Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole (1.1)
- Complicated Urinary Tract Infections (cUTI), Including Pyelonephritis (1.2)
- Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (1.3)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer all doses of ZERBAXA every 8 hours by intravenous infusion over 1 hour in patients 18 years or older. (2.1, 2.2)
- See Full Prescr bing Information for instructions on the preparation of solutions. (2.3)
- For doses above 1.5 g, reconstitute a second vial in the same manner as the first one, withdraw an appropriate volume (per Table 3 in the Full Prescr bing Information), and add to the same infusion bag. (2.3)

Recommended Dosage of ZERBAXA by Infection in Patients 18 years or older with Creatinine Clearance (CrCl) Greater than 50 mL/min (2.1)

Infection	Dose	Duration of Treatment
Complicated Intra-abdominal Infections (cIAI)*	1.5 g	4-14 days
Complicated Urinary Tract Infections (cUTI), Including Pyelonephritis	1.5 g	7 days
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	3 g	8-14 days

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

Recommended Dosage of ZERBAXA in Patients 18 years or older with CrCl 50 mL/min or less (2.2)

Estimated CrCl (mL/min)*	cIAI and cUTI, including pyelonephritis	HABP/VABP
30 to 50	ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours	ZERBAXA 1.5 g (1 g and 0.5 g) intravenously every 8 hours
15 to 29	ZERBAXA 375 mg (250 mg and 125 mg) intravenously every 8 hours	ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ZERBAXA 750 mg (500 mg and 250 mg) followed by a ZERBAXA 150 mg (100 mg and 50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest poss ble time following completion of dialysis)	A single loading dose of ZERBAXA 2.25 g (1.5 g and 0.75 g) followed by a ZERBAXA 450 mg (300 mg and 150 mg) maintenance dose administered every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

* CrCl estimated using Cockcroft-Gault formula

---------- DOSAGE FORMS AND STRENGTHS ----------

- ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection supplied as a sterile powder for reconstitution in single-dose vials containing ceftolozane 1 g (equivalent to 1.147 g ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g tazobactam sodium). (3)

----------CONTRAINDICATIONS----------

- ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Decreased efficacy was observed in a Phase 3 cIAI trial in a subgroup of patients with baseline CrCl of 30 to ≤50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly. (5.1)
- Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam ant bacterial drugs. Exercise caution in patients with known hypersensitivity to beta-lactam antibacterial drugs. If an anaphylactic reaction to ZERBAXA occurs, discontinue the drug and institute appropriate therapy. (5.2)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including ZERBAXA. Evaluate if diarrhea occurs. (5.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥5% in either cIAI or cUTI indication) are nausea, diarrhea, headache and pyrexia. The most common adverse reactions (≥5% in the HABP/VABP indication) are increase in hepatic transaminases, renal impairment/renal failure, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Geriatrics: Higher incidence of adverse reactions was observed in patients aged 65 years and older. In a Phase 3 cIAI trial, cure rates were lower in patients 65 years and older. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Complicated Intra-abdominal Infections

ZERBAXA used in combination with metronidazole is indicated for the treatment of patients 18 years and older with complicated intra-abdominal infections (cIAI) caused by the following susceptible 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*.

1.2 Complicated Urinary Tract Infections, Including Pyelonephritis

ZERBAXA is indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

1.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

ZERBAXA is indicated for the treatment of patients 18 years and older with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

1.4 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA should be used only to treat or prevent 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage 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 HABP/VABP administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older and with a creatinine clearance (CrCl) greater than 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 CrCl Greater than 50 mL/min

Infection	Dose	Frequency	Infusion Time (hours)	Duration of Treatment
Complicated Intra-abdominal Infections*	1.5 g	Every 8 Hours	1	4-14 days
Complicated Urinary Tract	1.5 g	Every 8 Hours	1	7 days

Infections, Including Pyelonephritis				
Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)	3 g	Every 8 Hours	1	8-14 days

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

2.2 Dosage Adjustments in Patients with Renal Impairment

Dose adjustment is required for patients with CrCl 50 mL/min or less (Table 2). All doses of ZERBAXA are administered over 1 hour. For patients with changing renal function, monitor CrCl at least daily and adjust the dosage of ZERBAXA accordingly *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Table 2: Dosage of ZERBAXA in Adult Patients with CrCl 50 mL/min or less

Estimated CrCl (mL/min)*	**Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis**	**Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/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 hemodialysis (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 (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)	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 treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

***** CrCl estimated using Cockcroft-Gault formula

2.3 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. For doses above 1.5 g, reconstitute a second vial in the same manner as the first one, withdraw an appropriate volume (per Table 3), and add to the same infusion bag.

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

2.4 Compatibility

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.

2.5 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 (36 to 46°F).

Constituted ZERBAXA solution or diluted ZERBAXA infusion should not be frozen.

3 DOSAGE FORMS AND STRENGTHS

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied as a white to yellow sterile powder for reconstitution in single-dose vials; each vial contains ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium).

4 CONTRAINDICATIONS

ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Efficacy in Patients with Baseline Creatinine Clearance of 30 to 50 mL/min

In a subgroup analysis of a Phase 3 cIAI trial, clinical cure rates were lower in patients with baseline CrCl of 30 to 50 mL/min compared to those with CrCl greater than 50 mL/min (Table 4). 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 cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of ZERBAXA accordingly *[see Dosage and Administration (2.2)]*.

Table 4: Clinical Cure Rates in a Phase 3 Trial of cIAI by Baseline Renal Function (MITT Population)

Baseline Renal Function	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
CrCl greater than 50 mL/min	312/366 (85.2)	355/404 (87.9)
CrCl 30 to 50 mL/min	11/23 (47.8)	9/13 (69.2)

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.

Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product 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 the drug and institute appropriate therapy.

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is confirmed, discontinue antibacterials not directed against *C. difficile*, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

5.4 Development of Drug-Resistant Bacteria

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

6 ADVERSE REACTIONS

The following serious reactions are described in greater detail in the Warnings and Precautions section:

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- *Clostridium difficile*-associated diarrhea *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and also may not reflect rates observed in practice.

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

ZERBAXA was evaluated in Phase 3 comparator-controlled clinical trials of cIAI and cUTI, which included a total of 1015 patients treated with ZERBAXA (1.5 g every 8 hours, adjusted based on renal function where appropriate) and 1032 patients treated with comparator (levofloxacin 750 mg daily in cUTI or meropenem 1 g every 8 hours in cIAI) for up to 14 days. The mean age of treated patients was 48 to 50 years (range 18 to 92 years), across treatment arms and indications. In both indications, about 25% of the subjects were 65 years of age or older. Most patients (75%) enrolled in the cUTI trial were female, and most patients (58%) enrolled in the cIAI trial were male. Most patients (>70%) in both trials were enrolled in Eastern Europe and were White.

The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA were nausea, diarrhea, headache, and pyrexia. Table 5 lists adverse reactions occurring in 1% or greater of patients receiving ZERBAXA in Phase 3 cIAI and cUTI clinical trials.

Table 5: Adverse Reactions Occurring in 1% or Greater of Patients Receiving ZERBAXA in Phase 3 cIAI and cUTI Clinical Trials

Preferred Term	Complicated Intra-abdominal Infections		Complicated Urinary Tract Infections, Including Pyelonephritis	
	ZERBAXA* (N=482) n (%)	Meropenem (N=497) n (%)	ZERBAXA* (N=533) n (%)	Levofloxacin (N=535) n (%)
Nausea	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
Headache	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
Diarrhea	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
Pyrexia	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
Constipation	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
Insomnia	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)
Vomiting	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
Hypokalemia	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
ALT increased	7 (1.5)	5 (1)	9 (1.7)	5 (0.9)
AST increased	5 (1)	3 (0.6)	9 (1.7)	5 (0.9)
Anemia	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
Thrombocytosis	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
Abdominal pain	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
Anxiety	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
Dizziness	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
Hypotension	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)
Atrial fibrillation	6 (1.2)	3 (0.6)	1 (0.2)	0
Rash	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)

* The ZERBAXA for injection dose was 1.5 g intravenously every 8 hours, adjusted to match renal function where appropriate. In the cIAI trials, ZERBAXA was given in conjunction with metronidazole.

Treatment discontinuation due to adverse events occurred in 2.0% (20/1015) of patients receiving ZERBAXA and 1.9% (20/1032) of patients receiving comparator drugs. Renal impairment (including the terms renal impairment, renal failure, and renal failure acute) led to discontinuation of treatment in 5/1015 (0.5%) subjects receiving ZERBAXA and none in the comparator arms.

Increased Mortality

In the cIAI trials (Phase 2 and 3), death occurred in 2.5% (14/564) of patients receiving ZERBAXA and in 1.5% (8/536) of patients receiving meropenem. The causes of death varied and included worsening and/or complications of infection, surgery and underlying conditions.

Less Common Adverse Reactions in Phase 3 cIAI and cUTI Clinical Trials

The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 1%:

Cardiac disorders: tachycardia, angina pectoris

Gastrointestinal disorders: gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic

General disorders and administration site conditions: infusion site reactions

Infections and infestations: candidiasis including oropharyngeal and vulvovaginal, fungal urinary tract infection
Investigations: increased serum gamma-glutamyl transpeptidase (GGT), increased serum alkaline phosphatase, positive Coombs test
Metabolism and nutrition disorders: hyperglycemia, hypomagnesemia, hypophosphatemia
Nervous system disorders: ischemic stroke
Renal and urinary system: renal impairment, renal failure
Respiratory, thoracic and mediastinal disorders: dyspnea
Skin and subcutaneous tissue disorders: urticaria
Vascular disorders: venous thrombosis

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

ZERBAXA was evaluated in a Phase 3 comparator-controlled clinical trial for HABP/VABP, which included a total of 361 patients treated with ZERBAXA (3 g every 8 hours, adjusted based on renal function where appropriate) and 359 patients treated with comparator (meropenem 1 g every 8 hours) for up to 14 days. The mean age of treated patients was 60 years (range 18 to 98 years), across treatment arms. About 44% of the subjects were 65 years of age or older. Most patients (71%) enrolled in the trial were male. All subjects were mechanically ventilated at randomization and 92% were in an intensive care unit (ICU) at randomization. The median APACHE II score was 17, and 33% of subjects had a baseline APACHE II score of ≥20, indicating a high severity of illness for many patients enrolled in this trial.

Table 6 lists adverse reactions occurring in 2% or greater of patients receiving ZERBAXA in a Phase 3 HABP/VABP clinical trial.

Table 6: Adverse Reactions Occurring in 2% or Greater of Patients Receiving ZERBAXA in a Phase 3 HABP/VABP Clinical Trial

Adverse Reactions	ZERBAXA* N=361 n (%)	Meropenem N=359 n (%)
Hepatic transaminase increased[1]	43 (11.9)	26 (7.2)
Renal impairment/renal failure[2]	32 (8.9)	22 (6.1)
Diarrhea	23 (6.4)	25 (7.0)
Intracranial hemorrhage[3]	16 (4.4)	5 (1.4)
Vomiting	12 (3.3)	10 (2.8)
Clostridium difficile colitis[4]	10 (2.8)	2 (0.6)

* The ZERBAXA for injection dose was 3 g intravenously every 8 hours, adjusted to match renal function where appropriate.
[1] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal.
[2] Includes acute renal failure, anuria, azotemia, oliguria, prerenal failure, renal failure, renal impairment.
[3] Includes cerebellar hemorrhage, cerebral hematoma, cerebral hemorrhage, hemorrhage intracranial, hemorrhagic stroke, hemorrhagic transformation stroke, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hematoma.
[4] Includes *Clostridium difficile* colitis, *Clostridium difficile* infection, *Clostridium* test positive.

Treatment discontinuation due to adverse reactions occurred in 1.1% (4/361) of patients receiving ZERBAXA and 1.4% (5/359) of patients receiving meropenem.

Less Common Adverse Reactions in a Phase 3 HABP/VABP Clinical Trial
The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 2%:

Investigations: blood alkaline phosphatase increased, gamma-glutamyltransferase increased, Coombs direct test positive

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 cUTI and cIAI 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 HABP/VABP clinical trial. In clinical trials, there was no evidence of hemolysis in patients who developed a positive direct Coombs test in any treatment group.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data available on ZERBAXA, ceftolozane or tazobactam use in pregnant women to allow assessment of a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal or fetal outcomes (see Data). Neither ceftolozane nor tazobactam produced embryo-fetal toxicity when administered to rodents during the period of organogenesis at ceftolozane doses approximately 3.5 times higher in mice and 2 times higher in rats than the maximum recommended human dose (MRHD) of 2 grams every 8 hours based on plasma AUC comparison or at tazobactam doses approximately 10 times higher in rats than the MRHD of 1 gram every 8 hours based on body surface area comparison. In pre-postnatal studies, where pregnant rats were administered intravenous ceftolozane or intraperitoneal tazobactam in gestation and through the lactation period, ceftolozane was associated with a decrease in auditory startle response in first generation offspring at a dose lower than the MRHD based on AUC comparison, and tazobactam was associated with reduced maternal body weight gain and increased still births at a dose equivalent to approximately 4 times the MRHD and reduced fetal body weights in first generation offspring at a dose approximately equivalent to the MRHD based on body surface area comparison (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

While available studies with multiple cephalosporins cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Ceftolozane

Embryo-fetal development studies were performed in mice administered intravenous ceftolozane at doses of 300, 1000, and 2000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 15) and in rats administered intravenous ceftolozane in doses of 100, 300, and 1000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 17). In mice ceftolozane was not associated with maternal or embryo-fetal toxicity with doses up to the highest dose of 2000 mg/kg/ day (approximately 3.5 times the MRHD of 2 grams every 8 hours based on plasma AUC comparison). In rats, no embryo-fetal toxicity was observed, but maternal body weight gain was reduced at a ceftolozane dose of 1000 mg/kg/day. No adverse maternal effects in rats were observed at a dose of 300 mg/kg/day and no

adverse embryo-fetal effects were observed at a dose of 1000 mg/kg/day (respectively equivalent to approximately 0.7- and 2-times the MRHD based on plasma AUC comparison).

In a pre-postnatal study in rats, intravenous ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal day 60 male pups at maternal doses greater than or equal to 300 mg/kg/day. No adverse effects were observed in rats at a dose of 100 mg/kg/day, a dose lower than the MRHD of 2 grams every 8 hours based on plasma AUC comparison.

Tazobactam

In an embryo-fetal study in rats, tazobactam was administered intravenously during the period of organogenesis (Gestation Day 7 through 17) at doses of 125, 500, and 3000 mg/kg/day. The high dose of 3000 mg/kg/day produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with fetal toxicity. No adverse maternal effects were observed at a dose of 500 mg/kg/day and no adverse fetal effects were observed at a dose of 3000 mg/kg/day (respectively equivalent to approximately 2- and 10-times the MRHD of 1 gram every 8 hours based on body surface area comparison). In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre-postnatal study in rats, tazobactam administered intraperitoneally in doses of 40, 320, and 1280 mg/kg/day at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) was associated with decreased maternal food consumption and body weight gain at the end of gestation and significantly more stillbirths at the high dose of 1280 mg/kg/day. No effects on the physical development, neurological function, or fertility and reproductive ability of first generation (F1) pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. The second generation (F2) fetuses were normal for all doses of tazobactam. No adverse effects on maternal reproduction were observed at doses up to 320 mg/kg/day and F1 body weights were not reduced at a dose of 40 mg/kg/day (respectively equivalent to approximately 1.0 and 0.1 times the MRHD of 1 gram every 8 hours based on body surface area comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of ceftolozane or tazobactam in human milk. There are no data on the effects of tazobactam or ceftolozane on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERBAXA and any potential adverse effects on the breastfed child from ZERBAXA or from the underlying maternal conditions.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1015 patients treated with ZERBAXA in the Phase 3 cIAI and cUTI clinical trials, 250 (24.6%) were 65 years or older, including 113 (11.1%) 75 years or older. The incidence of adverse events in both treatment groups was higher in older subjects (65 years or older) in the trials for both indications. In the cIAI trial, cure rates in the elderly (aged 65 years and older) in the ZERBAXA plus metronidazole arm were 69/100 (69%) and in the comparator arm were 70/85 (82.4%). This finding in the elderly population was not observed in the cUTI trial.

Of the 361 patients treated with ZERBAXA in the Phase 3 HABP/VABP clinical trial, 160 (44.3%) were 65 years or older, including 83 (23%) 75 years or older. The incidence of adverse events in both treatment groups was higher in older subjects (65 years or older). In the trial, Day 28 all-cause mortality rates in the elderly (aged 65 years and older) were comparable between treatment arms:50/160 (31.3%) in the ZERBAXA arm and 54/160 (33.8%) in the comparator arm.

ZERBAXA is substantially excreted by the kidney and the risk of adverse reactions to ZERBAXA may be greater in patients with renal impairment. 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 *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with CrCl 50 mL/min or less, including patients with ESRD on HD *[see Dosage and Administration (2.2), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

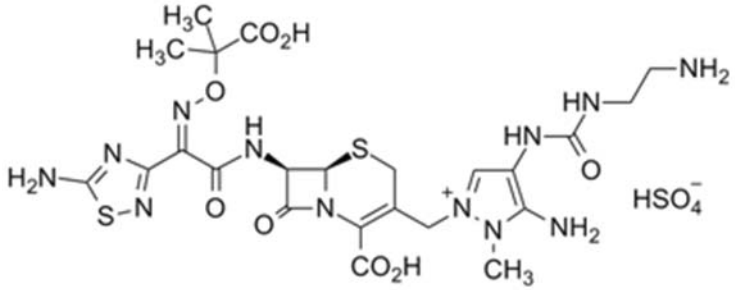
In the event of overdose, discontinue ZERBAXA and provide general supportive treatment. ZERBAXA can be removed by hemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the tazobactam metabolite M1 were removed by dialysis. No information is available on the use of hemodialysis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

11 DESCRIPTION

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

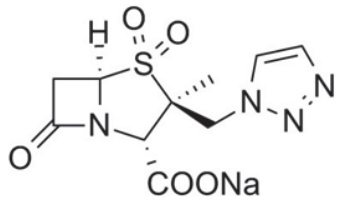
Ceftolozane sulfate is a semi-synthetic antibacterial drug of the beta-lactam class for parenteral administration. The chemical name of ceftolozane sulfate is 1*H*-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,sulfate (1:1). The molecular formula is $C_{23}H_{31}N_{12}O_8S_2^+ \bullet HSO_4^-$ and the molecular weight is 764.77.

Figure 1: Chemical structure of ceftolozane sulfate



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

Figure 2: Chemical structure of tazobactam sodium



ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is a white to yellow sterile powder for reconstitution consisting of ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium) per vial, packaged in single-dose glass vials. The product contains sodium chloride (487 mg/vial) as a stabilizing agent, citric acid (21 mg/vial), and L-arginine (approximately 600 mg/vial) as excipients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZERBAXA is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

As with other beta-lactam antibacterial agents, the percent time of dosing interval that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism has been shown to be the best predictor of efficacy in animal models of infection. The percent time of dosing interval that the plasma concentration of tazobactam exceeds a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in *in vitro* and *in vivo* models. The exposure-response analyses in efficacy and safety clinical trials for cIAI, cUTI, and HABP/VABP support the recommended dose regimens of ZERBAXA.

Cardiac Electrophysiology

In a randomized, positive and placebo-controlled crossover thorough QTc study, 51 healthy subjects were administered a single therapeutic dose of ZERBAXA 1.5 gram (ceftolozane 1 g and tazobactam 0.5 g) and a supratherapeutic dose of ZERBAXA 4.5 gram (ceftolozane 3 g and tazobactam 1.5 g). No significant effects of ZERBAXA on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected.

12.3 Pharmacokinetics

Ceftolozane and tazobactam pharmacokinetics are similar following single- and multiple-dose administrations. The C_{max} and AUC of ceftolozane and tazobactam increase in proportion to dose.

The mean steady-state population pharmacokinetic parameters of ZERBAXA in patients with cIAI and cUTI receiving 1-hour intravenous infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or patients with HABP/VABP receiving 1-hour intravenous infusions of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) every 8 hours are summarized in Table 7.

Table 7: Mean (SD) 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 Greater than 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 HABP/VABP Patients	
	Ceftolozane (n=317)	Tazobactam (n=244)	Ceftolozane (n=247)	Tazobactam (n=247)
C_{max} (mcg/mL)	65.7 (27)	17.8 (9)	105 (46)	26.4 (13)
$AUC_{0\text{-}8,ss}$ (mcg•h/mL)	186 (74)	35.8 (57)	392 (236)	73.3 (76)

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 pneumonia (N=22), mean pulmonary epithelial lining fluid-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). Minimum ceftolozane and tazobactam epithelial lung lining fluid concentrations in ventilated subjects at the end of the dosing interval were 8.2 mcg/mL and 1.0 mcg/mL, respectively.

Elimination

Ceftolozane is eliminated from the body by renal excretion with a mean half-life of approximately 3 to 4 hours. Tazobactam is eliminated by renal excretion and metabolism with a plasma mean half-life of approximately 2 to 3 hours. The elimination half-life ($t_{1/2}$) of ceftolozane or tazobactam is independent of dose.

Metabolism

Ceftolozane does not appear to be metabolized to any appreciable extent and is not a substrate for CYP enzymes. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1.

Excretion

Ceftolozane, tazobactam and the tazobactam metabolite M1 are excreted 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 drug. 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 – 6.69 L/h) was similar to plasma CL (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. Tazobactam is a substrate for OAT1 and OAT3 transporters and its elimination has been shown to be inhibited by probenecid, an inhibitor of OAT1/3.

Specific Populations

Dose adjustment is not warranted on the basis of age (18 years and older), gender, or race/ethnicity. No significant differences in the pharmacokinetics of ceftolozane and tazobactam were observed based on age (18 years and older), gender, weight, or race/ethnicity.

Patients with Renal Impairment

The ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in subjects with CrCl 80-51 mL/min, 50-30 mL/min, and 29-15 mL/min, 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 Dosage and Administration (2.2)]*.

In subjects with ESRD on HD, approximately two-thirds of the administered ZERBAXA dose is removed by HD. A single loading dose of Zerbaxa followed by maintenance dose administered every 8 hours for the remainder of the treatment period is recommended in patients with ESRD on HD. On HD days, administer the dose at the earliest possible time following completion of HD. *[See Dosage and Administration (2.2).]*

Patients with Augmented Renal Function

Following a single 1 hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) to critically-ill patients 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. No dose adjustment of ZERBAXA is recommended for HABP/VABP patients with augmented renal function *[see Clinical Studies (14.3)]*.

Patients with Hepatic Impairment

As ZERBAXA does not undergo hepatic metabolism, the systemic clearance of ZERBAXA is not expected to be affected by hepatic impairment.

No dose adjustment is recommended for ZERBAXA in subjects with hepatic impairment.

Geriatric Patients

In a population pharmacokinetic analysis of ZERBAXA, no clinically relevant differences in exposure were observed with regard to age.

No dose adjustment of ZERBAXA based on age is recommended. Dosage adjustment for ZERBAXA in geriatric patients should be based on renal function *[see Dosage and Administration (2.2)]*.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Drug Interactions

No drug-drug interaction was observed between ceftolozane and tazobactam in a clinical study in 16 healthy subjects. *In vitro* and *in vivo* data indicate that ZERBAXA is unlikely to cause clinically relevant drug-drug interactions related to CYPs and transporters at therapeutic concentrations.

Drug Metabolizing Enzymes

In vivo data indicated that ZERBAXA is not a substrate for CYPs. Thus, clinically relevant drug-drug interactions involving inhibition or induction of CYPs by other drugs are unlikely to occur.

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. *In vitro* induction studies in primary human hepatocytes demonstrated that ceftolozane, tazobactam, and the tazobactam metabolite M1 decreased CYP1A2 and CYP2B6 enzyme activity and mRNA levels in primary human hepatocytes as well as CYP3A4 mRNA levels at supratherapeutic plasma concentrations. Tazobactam metabolite M1 also decreased CYP3A4 activity at supratherapeutic plasma concentrations. A clinical drug-drug interaction study was conducted and results indicated drug interactions involving CYP1A2 and CYP3A4 inhibition by ZERBAXA are not anticipated.

Membrane Transporters

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic concentrations.

Tazobactam is a known substrate for OAT1 and OAT3. Co-administration of tazobactam with the OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71%. Co-administration of ZERBAXA with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam 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. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. A clinical drug-drug interaction study was conducted and results indicated clinically relevant drug interactions involving OAT1/OAT3 inhibition by ZERBAXA are not anticipated.

12.4 Microbiology

Mechanism of Action

Ceftolozane belongs to the cephalosporin class of antibacterial drugs. The bactericidal action of ceftolozane results from inhibition of cell wall biosynthesis, and is mediated through binding to penicillin-binding proteins (PBPs). Ceftolozane is an inhibitor of PBPs of *P. aeruginosa* (e.g., PBP1b, PBP1c, and PBP3) and *E. coli* (e.g., PBP3).

Tazobactam sodium has little clinically relevant *in vitro* activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is an irreversible inhibitor of some beta-lactamases (e.g., certain penicillinases and cephalosporinases), and can bind covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases.

Resistance

Mechanisms of beta-lactam resistance may include the production of beta-lactamases, modification of PBPs by gene acquisition or target alteration, up-regulation of efflux pumps, and loss of outer membrane porin.

Clinical isolates may produce multiple beta-lactamases, express varying levels of beta-lactamases, or have amino acid sequence variations, and other resistance mechanisms that have not been identified.

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

ZERBAXA demonstrated *in vitro* activity against Enterobacteriaceae in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, and OXA. ZERBAXA is not active against bacteria that produce serine carbapenemases [*K. pneumoniae* carbapenemase (KPC)], and metallo-beta-lactamases.

In ZERBAXA clinical trials, some isolates of Enterobacteriaceae with minimum inhibitory concentration to ZERBAXA of ≤2 mcg/mL produced beta-lactamases. These isolates produced one or more beta-lactamases of the following enzyme groups: CTX-M, OXA, TEM, or SHV.

Some of these beta-lactamases were also produced by isolates of Enterobacteriaceae with minimum inhibitory concentration to ZERBAXA >2 mcg/mL.

ZERBAXA demonstrated *in vitro* activity against *P. aeruginosa* isolates tested that had chromosomal AmpC, loss of outer membrane porin (OprD), or up regulation of efflux pumps (MexXY, MexAB).

Isolates resistant to other cephalosporins may be susceptible to ZERBAXA, although cross-resistance may occur.

Interaction with Other Antimicrobials

In vitro synergy studies suggest no antagonism between ZERBAXA and other antibacterial drugs (e.g., meropenem, amikacin, aztreonam, levofloxacin, tigecycline, rifampin, linezolid, daptomycin, vancomycin, and metronidazole).

Antimicrobial Activity

ZERBAXA has been shown to be active against the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

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*

Anaerobic bacteria:
- *Bacteroides fragilis*

Complicated Urinary Tract Infections, Including Pyelonephritis

Gram-negative bacteria:
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*

Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

Gram-negative bacteria:
- *Enterobacter cloacae*
- *Escherichia coli*
- *Haemophilus influenzae*

Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftolozane and tazobactam against isolates of similar genus or organism group. However, the efficacy of ZERBAXA in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria:
Citrobacter koseri
Klebsiella aerogenes
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia liquefaciens

Gram-positive bacteria:
Streptococcus agalactiae
Streptococcus intermedius

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for ceftolozane and tazobactam, please see:
https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an *in vitro* mouse lymphoma assay and an *in vivo* rat bone-marrow micronucleus assay. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, an *in vitro* mouse lymphoma assay, an *in vitro* HPRT assay in Chinese hamster ovary cells, an *in vivo* mouse micronucleus assay, and an *in vivo* unscheduled DNA synthesis (UDS) assay.

Tazobactam was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, an *in vitro* mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an *in vivo* mouse bone-marrow micronucleus assay, and an *in vivo* UDS assay.

Ceftolozane was administered in a fertility study at intravenous doses of 100, 300, and 1000 mg/kg/day to male rats for 28 days before mating and through the mating period and to female rats for 14 days before mating, through the mating period, and until the 7th day of gestation. Ceftolozane had no adverse effect on fertility in male or female rats at doses up to 1000 mg/kg/day (approximately 1.4 times the maximum recommended human dose (MHRD) of 2 grams every 8 hours based on AUC comparison).

In a rat fertility study, intraperitoneal tazobactam doses of 40, 160, and 640 mg/kg/day were administered twice-daily, to male rats beginning 70 days before mating and through the mating period, and to female rats beginning 14 days before mating, during the mating period, and until Gestation Day 21. Male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 2 times the MRHD of 1 gram every 8 hours based on body surface comparison).

14 CLINICAL STUDIES

14.1 Complicated Intra-abdominal Infections

A total of 979 adults hospitalized with cIAI were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) intravenously every 8 hours plus metronidazole (500 mg intravenously every 8 hours) to meropenem (1 g intravenously every 8 hours) for 4 to 14 days of therapy. Complicated intra-abdominal infections included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis. The majority of patients (75%) were from Eastern Europe; 6.3% were from the United States.

The primary efficacy endpoint was clinical response, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-cure (TOC) visit which occurred 24 to 32 days after the first dose of study drug. The primary efficacy analysis population was the microbiological intent-to-treat (MITT) population, which included all patients who had at least 1 baseline intra-abdominal pathogen regardless of the susceptibility to study drug. The key secondary efficacy endpoint was clinical response at the TOC visit in the microbiologically evaluable (ME) population, which included all protocol-adherent MITT patients.

The MITT population consisted of 806 patients; the median age was 52 years and 57.8% were male. The most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 47% of patients. Diffuse peritonitis at baseline was present in 34.2% of patients.

ZERBAXA plus metronidazole was non-inferior to meropenem with regard to clinical cure rates at the TOC visit in the MITT population. Clinical cure rates at the TOC visit are displayed by patient population in Table 8. Clinical cure rates at the TOC visit by pathogen in the MITT population are presented in Table 9.

Table 8: Clinical Cure Rates in a Phase 3 Trial of Complicated Intra-Abdominal Infections

Analysis Population	ZERBAXA plus metronidazole* n/N (%)	Meropenem† n/N (%)	Treatment Difference (95% CI)‡
MITT	323/389 (83)	364/417 (87.3)	-4.3 (-9.2, 0.7)
ME	259/275 (94.2)	304/321 (94.7)	-0.5 (-4.5, 3.2)

* ZERBAXA 1.5 g intravenously every 8 hours + metronidazole 500 mg intravenously every 8 hours

† 1 gram intravenously every 8 hours

‡ The 95% confidence interval (CI) was calculated as an unstratified Wilson Score CI.

Table 9: Clinical Cure Rates by Pathogen in a Phase 3 Trial of Complicated Intra-abdominal Infections (MITT Population)

Organism Group Pathogen	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Aerobic Gram-negative		
Escherichia coli	216/255 (84.7)	238/270 (88.1)
Klebsiella pneumoniae	31/41 (75.6)	27/35 (77.1)
Pseudomonas aeruginosa	30/38 (79)	30/34 (88.2)
Enterobacter cloacae	21/26 (80.8)	24/25 (96)
Klebsiella oxytoca	14/16 (87.5)	24/25 (96)
Proteus mirabilis	11/12 (91.7)	9/10 (90)
Aerobic Gram-positive		
Streptococcus anginosus	26/36 (72.2)	24/27 (88.9)
Streptococcus constellatus	18/24 (75)	20/25 (80)
Streptococcus salivarius	9/11 (81.8)	9/11 (81.8)
Anaerobic Gram-negative		
Bacteroides fragilis	42/47 (89.4)	59/64 (92.2)
Bacteroides ovatus	38/45 (84.4)	44/46 (95.7)
Bacteroides thetaiotaomicron	21/25 (84)	40/46 (87)
Bacteroides vulgatus	12/15 (80)	24/26 (92.3)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cIAI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 53/601 (9%). Cure rates in this subset were similar to the overall trial results. *In vitro* susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC ≤ 2 mcg/mL), while some others were not susceptible (MIC >2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

14.2 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 1068 adults hospitalized with cUTI (including pyelonephritis) were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) intravenously every 8 hours to levofloxacin (750 mg intravenously once daily) for 7 days of therapy. The primary efficacy endpoint was defined as complete resolution or marked improvement of the clinical symptoms and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) at the test-of-cure (TOC) visit 7 (± 2) days after the last dose of study drug. The primary efficacy analysis population was the microbiologically modified intent-to-treat (mMITT) population, which included all patients who received study medication and had at least 1 baseline uropathogen. The key secondary efficacy endpoint was the composite microbiological and clinical cure response at the TOC visit in the microbiologically evaluable (ME) population, which included protocol-adherent mMITT patients with a urine culture at the TOC visit.

The mMITT population consisted of 800 patients with cUTI, including 656 (82%) with pyelonephritis. The median age was 50.5 years and 74% were female. Concomitant bacteremia was identified in 62 (7.8%) patients at baseline; 608 (76%) patients were enrolled in Eastern Europe and 14 (1.8%) patients were enrolled in the United States.

ZERBAXA demonstrated efficacy with regard to the composite endpoint of microbiological and clinical cure at the TOC visit in both the mMITT and ME populations (Table 10). Composite microbiological and clinical cure rates at the TOC visit by pathogen in the mMITT population are presented in Table 11.

In the mMITT population, the composite cure rate in ZERBAXA-treated patients with concurrent bacteremia at baseline was 23/29 (79.3%).

Although a statistically significant difference was observed in the ZERBAXA arm compared to the levofloxacin arm with respect to the primary endpoint, it was likely attributable to the 212/800 (26.5%) patients with baseline organisms non-susceptible to levofloxacin. Among patients infected with a levofloxacin-susceptible organism at baseline, the response rates were similar (Table 10).

Table 10: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections

Analysis Population	ZERBAXA* n/N (%)	Levofloxacin† n/N (%)	Treatment Difference (95% CI)‡
mMITT	306/398 (76.9)	275/402 (68.4)	8.5 (2.3, 14.6)
Levofloxacin resistant baseline pathogen(s)	60/100 (60)	44/112 (39.3)	
No levofloxacin resistant baseline pathogen(s)	246/298 (82.6)	231/290 (79.7)	
ME	284/341 (83.3)	266/353 (75.4)	8.0 (2.0, 14.0)

* ZERBAXA 1.5 g intravenously every 8 hours
† 750 mg intravenously once daily
‡ The 95% confidence interval was based on the stratified Newcombe method.

Table 11: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections, in Subgroups Defined by Baseline Pathogen (mMITT Population)

Pathogen	ZERBAXA n/N (%)	Levofloxacin n/N (%)
Escherichia coli	247/305 (81)	228/324 (70.4)
Klebsiella pneumoniae	22/33 (66.7)	12/25 (48)
Proteus mirabilis	11/12 (91.7)	6/12 (50)
Pseudomonas aeruginosa	6/8 (75)	7/15 (46.7)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cUTI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 104/687 (15%). Cure rates in this subset were similar to the overall trial results. *In vitro* susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC ≤2 mcg/mL), while some others were not susceptible (MIC >2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

14.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP)

A total of 726 adult patients hospitalized with HABP/VABP were enrolled in a multinational, double-blind study (NCT02070757) comparing ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) intravenously every 8 hours to meropenem (1 g intravenously every 8 hours) for 8 to 14 days of therapy. All patients had to be intubated and on mechanical ventilation at randomization.

Efficacy was assessed based on all-cause mortality at Day 28 and clinical cure, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-

cure (TOC) visit which occurred 7 to 14 days after the end of treatment. The analysis population was the intent-to-treat (ITT) population, which included all randomized patients.

Following a diagnosis of HABP/VABP and prior to receipt of first dose of study drug, if required, patients could have received up to a maximum of 24 hours of active non-study antibacterial drug therapy in the 72 hours preceding the first dose of study drug. Patients who had failed prior antibacterial drug therapy for the current episode of HABP/VABP could be enrolled if the baseline lower respiratory tract (LRT) culture showed growth of a Gram-negative pathogen while the patient was on the antibacterial therapy and all other eligibility criteria were met. Empiric therapy at baseline with linezolid or other approved therapy for Gram-positive coverage was required in all patients pending baseline LRT culture results. Adjunctive Gram-negative therapy was optional and allowed for a maximum of 72 hours in centers with a prevalence of meropenem-resistant *P. aeruginosa* more than 15%.

Of the 726 patients in the ITT population the median age was 62 years and 44% of the population was 65 years of age and older, with 22% of the population 75 years of age and older. The majority of patients were white (83%), male (71%) and were from Eastern Europe (64%). The median APACHE II score was 17 and 33% of subjects had a baseline APACHE II score of greater than or equal to 20. All subjects were on mechanical ventilation and 519 (71%) had VABP. At randomization, 92% of subjects were in the ICU, 77% had been hospitalized for 5 days or longer, and 49% were ventilated for 5 days or longer. A total of 258 of 726 (36%) patients had CrCl less than 80 mL/min at baseline; among these, 99 (14%) had CrCl less than 50 mL/min. Patients with end-stage renal disease (CrCl less than 15 mL/min) were excluded from the trial. Approximately 13% of subjects were failing their current antibacterial drug therapy for HABP/VABP, and bacteremia was present at baseline in 15% of patients. Key comorbidities included diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease at rates of 22%, 16%, and 12%, respectively. In both treatment groups, most subjects (63.1%) received between 8 and 14 days of study therapy as specified in the protocol.

Table 12 presents the results for Day 28 all-cause mortality and clinical cure at the TOC visit overall and by ventilated HABP and VABP.

Table 12: Day 28 All-cause Mortality and Clinical Cure Rates at TOC from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (ITT Population)

Endpoint	ZERBAXA	Meropenem	Treatment Difference (95% CI)*
Day 28 All-cause Mortality	87/362 (24.0)	92/364 (25.3)	1.1 (-5.13, 7.39)
VABP	63/263 (24.0)	52/256 (20.3)	-3.6 (-10.74, 3.52)
Ventilated HABP	24/99 (24.2)	40/108 (37.0)	12.8 (0.18, 24.75)
Clinical Cure at TOC Visit	197/362 (54.4)	194/364 (53.3)	1.1 (-6.17, 8.29)
VABP	147/263 (55.9)	146/256 (57.0)	-1.1 (-9.59, 7.35)
Ventilated HABP	50/99 (50.5)	48/108 (44.4)	6.1 (-7.44, 19.27)

*The CI for overall treatment difference was based on the stratified Newcombe method with minimum risk weights. The CI for treatment difference of each primary diagnosis was based on the unstratified Newcombe method.

In the ITT population, Day 28 all-cause mortality and clinical cure rates in patients with CrCl greater than or equal to 150 mg/mL were similar between ZERBAXA and meropenem. In patients with bacteremia at baseline, Day 28 all-cause mortality rates were 23/64 (35.9%) for ZERBAXA-treated patients and 13/41 (31.7%) for meropenem-treated patients; clinical cure rates were 30/64 (46.9%) and 15/41 (36.6%), respectively.

Per pathogen Day 28 all-cause mortality and clinical cure at TOC were assessed in the microbiologic intention to treat population (mITT), which consisted of all randomized subjects who had a baseline lower respiratory tract (LRT) pathogen that was susceptible to both study treatments. In the mITT population, *Klebsiella pneumoniae* (113/425, 26.6%) and *Pseudomonas aeruginosa* (103/425, 24.2%) were the most prevalent pathogens isolated from baseline LRT cultures.

Day 28 all-cause mortality and clinical cure rates at TOC by pathogen in the mITT population are presented in Table 13. In the mITT population, clinical cure rates in patients with a Gram-negative

pathogen at baseline were 139/215 (64.7%) for ZERBAXA and 115/204 (56.4%) for meropenem, respectively.

Table 13: Day 28 All-cause Mortality and Clinical Cure Rates at TOC by Baseline Pathogen from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP) (mITT population)

Baseline Pathogen Category Baseline Pathogen	Day 28 All-cause Mortality		Clinical Cure at TOC	
	ZERBAXA n/N (%)	Meropenem n/N (%)	ZERBAXA n/N (%)	Meropenem n/N (%)
Pseudomonas aeruginosa	12/47 (25.5)	10/56 (17.9)	29/47 (61.7)	34/56 (60.7)
Enterobacteriaceae	27/161 (16.8)	42/157 (26.8)	103/161 (64.0)	87/157 (55.4)
Enterobacter cloacae	2/15 (13.3)	8/14 (57.1)	8/15 (53.3)	4/14 (28.6)
Escherichia coli	10/50 (20.0)	11/42 (26.2)	32/50 (64.0)	26/42 (61.9)
Klebsiella oxytoca	3/14 (21.4)	3/12 (25.0)	9/14 (64.3)	7/12 (58.3)
Klebsiella pneumoniae	7/51 (13.7)	13/62 (21.0)	34/51 (66.7)	39/62 (62.9)
Proteus mirabilis	5/22 (22.7)	5/18 (27.8)	13/22 (59.1)	11/18 (61.1)
Serratia marcescens	3/14 (21.4)	1/12 (8.3)	8/14 (57.1)	7/12 (58.3)
Haemophilus influenzae	0/20 (0)	2/15 (13.3)	17/20 (85.0)	8/15 (53.3)

In a subset of Enterobacteriaceae isolates from both arms of the trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 101/425 (23.8%). Day 28 all-cause mortality and clinical cure rates in this subset were similar to the overall trial results.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied in single-dose vials containing ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium) per vial. Vials are supplied in cartons containing 10 vials.

(NDC 67919-030-01)

16.2 Storage and Handling

ZERBAXA vials should be stored refrigerated at 2 to 8°C (36 to 46°F) and protected from light.

The reconstituted solution, once diluted, may be stored for 24 hours at room temperature or for 7 days under refrigeration at 2 to 8° C (36 to 46°F).

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patient that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask patient about any previous hypersensitivity reactions to ZERBAXA, other beta-lactams (including cephalosporins) or other allergens *[see Warnings and Precautions (5.2)]*.

Potentially Serious Diarrhea

Advise patient that diarrhea is a common problem caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell patient to contact his or her healthcare provider *[see Warnings and Precautions (5.3)]*.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including ZERBAXA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZERBAXA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better

early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZERBAXA or other antibacterial drugs in the future *[see Warnings and Precautions (5.4)]*.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: Steri-Pharma, LLC
Syracuse, NY 13202, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk7625a-iv-1906r004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829sOrig1s008

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 206829/S-008
Priority or Standard	Priority
Submit Date(s)	December 3, 2018
Received Date(s)	December 3, 2018
PDUFA Goal Date	June 3, 2019
Division/Office	Division of Anti-Infective Products/Office of Antimicrobial Products
Review Completion Date	May 29, 2019
Established/Proper Name	ceftolozane/tazobactam
Trade Name	ZERBAXA
Pharmacologic Class	Cephalosporin plus Beta-lactamase inhibitor
Applicant	Merck and Co., Inc., on behalf of Cubist Pharmaceuticals, LLC
Dosage form	Intravenous
Applicant proposed Dosing Regimen	3 g every 8 hours (two vials of 1.5 g every 8 hours)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Regulatory Action	Approval
Indication(s)/Population(s) (if applicable)	Treatment of hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	3 g every 8 hours (two vials of 1.5 g of Zerbaxa every 8 hours)

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Deborah Wang, PharmD
Chief, Regulatory Project Management Staff	Maureen Dillon-Parker, MS
Nonclinical Reviewer	James Wild, PhD
Nonclinical Team Leader	Terry Miller, PhD
Office of Clinical Pharmacology Reviewer	Anthony Nicasio, PharmD
Office of Clinical Pharmacology Reviewer (Pharmacometrics)	Jason Moore, PharmD
Office of Clinical Pharmacology Team Leader	Seong Jang, PhD
Clinical Microbiology Reviewer	Kerian Grande-Roche, PhD
Clinical Microbiology Team Leader	Avery Goodwin, PhD
Clinical Reviewer	Maria Allende, MD
Clinical Team Leader	Peter Kim, MD, MS
Statistical Reviewer	Cheryl Dixon, PhD
Statistical Team Leader	Karen Higgins, ScD
Cross-Discipline Team Leader	Peter Kim, MD, MS
Division Director (DAIP)	Sumathi Nambiar, MD, MPH

Additional Reviewers of Application

OPQ	Gurpreet Gill-Sangha, PhD
OPDP	David Foss, PharmD, MPH/James Dvorsky, PharmD
OSI	Aisha Johnson, MD, MPH, MBA/Min Lu, MD, MPH
Other	

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	James Wild, PhD	OAP/DAIP	Sections: 4.2, 5, 15.3	**Select one:** _X_ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Terry Miller, PhD	OAP/DAIP	Sections: 4.2, 5, 15.3	**Select one:** ___ Authored _X_ Approved
	Signature:			
Clinical Pharmacology Reviewer	Anthony Nicasio, PharmD	OCP/DCPIV	Sections: 6, 15.4	**Select one:** _X_ Authored ___ Approved
	Signature:			
Clinical Pharmacology Reviewer	Jason Moore, PharmD	OCP/DCPIV	Section: 15.4.2	**Select one:** _X_ Authored ___ Approved
	Signature:			
Clinical Pharmacology Team Leader	Seong Jang, PhD	OCP/DCPIV	Section: 6, 15.4	**Select one:** ___ Authored _X_ Approved
	Signature:			
Clinical Microbiology Reviewer	Kerian Grande-Roche, PhD	OAP/DAIP	Section: 4.3, 15.6	**Select one:** _X_ Authored ___ Approved
	Signature:			

Signatures (continued)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Microbiology Team Leader	Avery Goodwin, PhD	OAP/DAIP	Section: 4.3, 15.6	**Select one:** ___ Authored _X_ Approved
	Signature:			
Clinical Reviewer	Maria Allende, MD	OAP/DAIP	Sections: 1.1, 1.2, 2, 4.1, 7, 8.2, 8.4, 9, 10, 11, 13, 15.1, 15.2, 15.5	**Select one:** _X_ Authored ___ Approved
	Signature:			
Clinical Team Leader	Peter Kim, MD, MS	OAP/DAIP	Sections: 1 (authored), 1.1, 1.2,2, 3,4.1, 7, 8.2, 8.2.11 (authored), 8.4 (authored), 9,10,11 (authored),12,13 (authored),14, 15.1, 15.2, 15.5	**Select one:** ___ Authored _X_ Approved
	Signature:			
Statistical Reviewer	Cheryl Dixon, PhD	OB/DBIV	Sections: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature:			
Statistical Team Leader	Karen Higgins, ScD	OB/DBIV	Section: 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature:			

Signatures (continued)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Associate Director for Labeling	Abimbola Adebowale, PhD	OAP/DAIP	Section: 11	**Select one:** ___ Authored ___ Acknowledged __X__ Approved
	Signature:			
Regulatory Project Manager	Deborah Wang, PharmD	OAP/DAIP	Section: 3	**Select one:** ___ Authored ___ Acknowledged __X__ Approved
	Signature:			
Chief, Regulatory Project Management Staff	Maureen Dillon-Parker, MS	OAP/DAIP	Section: 3	**Select one:** ___ Authored ___ Acknowledged __X__ Approved
	Signature:			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ceftolozane/tazobactam (TOL/TAZ) (Zerbaxa) (all of these terms are used in this review and refer to the same drug product) is a fixed drug combination product containing a cephalosporin ceftolozane and tazobactam, a β-lactamase inhibitor (BLI), originally approved on December 29, 2014 for use in adult patients with cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. Zerbaxa is currently approved for the following indications.

- Complicated intra-abdominal infections, used in combination with metronidazole, caused by: *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus*, or *Streptococcus salivarius*
- Complicated urinary tract infections, including pyelonephritis caused by: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*.

In this supplemental NDA (sNDA), the Applicant is seeking an indication for: "*the treatment of* (b) (4) The Division's recommended indication is for the treatment of hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP). For the purposes of this review, HABP and ventilated HABP (vHABP) will be used interchangeably. The Applicant's proposed dosage regimen of Zerbaxa for treatment of HABP/VABP is 3 g administered q8h by IV infusion over 1 hour in patients 18 years of age and older (b) (4)

This sNDA does not contain any updates to the Chemistry, Manufacturing and Controls sections of the dossier.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence to support the safety and efficacy of ceftolozane/tazobactam for the treatment of VABP/vHABP is from the Phase 3 HABP/VABP trial, PN008MK7625A. A single adequate and well-controlled Phase 3 trial was accepted to provide evidence of effectiveness for ceftolozane/tazobactam for the treatment of VABP/vHABP since ceftolozane/tazobactam is already approved for 2 other infectious disease indications: complicated intra-abdominal infections and complicated urinary tract infections.

The results of PN008MK7625A demonstrated non-inferiority of ceftolozane/tazobactam to meropenem for the primary endpoint of Day 28 all-cause mortality. The key secondary endpoint of clinical response at the TOC visit, as well as, additional subgroup and sensitivity analyses supported the finding of noninferiority. One limitation to the generalizability of the results is the lack of ethnic and racial diversity due to the enrollment of sites primarily outside of the United States.

1.3. Cross-Discipline Team Leader Assessment

The Applicant has provided substantial evidence for the effectiveness of TOL/TAZ for the treatment of HABP/VABP. TOL/TAZ was noninferior to meropenem for the primary endpoint of 28-day all-cause mortality which was 24.0% in the TOL/TAZ arm versus 25.3% in the meropenem arm for a treatment difference (stratified 2-sided 95% CI) of 1.1% (-5.1, 7.4%). The key secondary endpoint, clinical cure, supported the finding of noninferiority. The clinical cure rate at the TOC visit was 54.4% in the TOL/TAZ group versus 53.3% in the meropenem group. The overall treatment difference (stratified 2-sided 95% CI) was 1.1% (-6.2, 8.3%).

CDTL comment: I concur with the review team's assessment that TOL/TAZ was noninferior to meropenem for the treatment of HABP/VABP.

The safety population for P008 included a total of 361 patients treated with TOL/TAZ (3 g every 8 hours, adjusted based on renal function where appropriate) and 359 patients treated with comparator (meropenem 1 g every 8 hours, adjusted based on renal function) for up to 14 days. The mean age of treated patients was 60 years (range 18 to 98 years), across treatment arms. Approximately 44% of the subjects were 65 years of age or older. Most patients (71%) enrolled in the trial were male. All subjects were mechanically ventilated at randomization and 92% were in an intensive care unit (ICU) at randomization. The median APACHE II score was 17, and 33% of subjects had a baseline APACHE II score of ≥20, indicating a high severity of illness for many patients enrolled in this trial.

Dr. Allende, the clinical reviewer, concluded that the safety and efficacy of TOL/TAZ are acceptable for approval of TOL/TAZ for the HABP/VABP treatment indication. She has raised concerns of adverse events related to intracranial hemorrhage, hepatotoxicity, and nephrotoxicity and has recommended that these issues be communicated under the Warnings and Precautions section of the Zerbaxa product label. She has also recommended a post-marketing study to assess the effect of TOL/TAZ on platelet function.

Below, I have provided a summary of these specific adverse events, my assessment and recommendations for labeling.

Intracranial hemorrhage:

Regarding intracranial hemorrhage, 4.4% (16/361) of TOL/TAZ -treated patients and 1.4% (5/359) of meropenem-treated patients experienced an intracranial hemorrhage. Among these patients, 15/16 TOL/TAZ-treated patients and 4/5 meropenem-treated patients died. The cause for the imbalance in intracranial hemorrhage was not established.

Twenty-four suspected cases of intracranial hemorrhage were initially identified early in the review (18 from the TOL/TAZ arm and 6 from the meropenem arm). This was later revised to 21 cases, 16 on TOL/TAZ and 5 on meropenem (1 TOL/TAZ subject was subsequently determined to have an ischemic stroke without hemorrhagic conversion, and 1 TOL/TAZ and 1 meropenem subject each had brain herniation without definitive evidence of CNS hemorrhage). It is important to note that out of the original 24 subjects, 23 had a medical history related to either cerebral bleeding/injury (79.2%) or cerebral ischemia (16.7%) prior to entering the study. All 16 TOL/TAZ subjects had medical histories consistent with predisposing factors for cerebral hemorrhage, that is, recent intracranial hemorrhage, head trauma, and/or ischemic stroke. The Applicant's hematology consultants noted that there was no obvious consistent coagulopathy based on laboratory data and that the observed abnormalities had reasonable explanations related to underlying diseases, e.g., liver disease or administration of antithrombotic agents. Normal INR/PT values were found in the majority of subjects and therefore suggested no direct effect on vitamin K metabolism. Normal platelet counts while in the study suggested no effects on platelets. The observed mild thrombocytopenia in some cases was likely due to underlying diseases. The Applicant's consultants noted that the observed CNS hemorrhages were most likely related to complications of the underlying diagnoses and the complications of management of the underlying diseases. There was no pattern of timing of study drug to the occurrence of the CNS hemorrhage AEs/SAEs. Neither consultant could specifically comment on whether TOL/TAZ caused platelet dysfunction as this was not assessed during the trial. One consultant did note that there was no published evidence that TOL/TAZ impairs platelet dysfunction.

In response to FDA's query regarding assessment of platelet function with TOL/TAZ, the Applicant stated that no studies had been conducted to assess the impact of TOL/TAZ on platelet function. They also stated that they were not aware of any published literature on the topic. They noted that in nonclinical repeat dose studies with ceftolozane alone or with TOL/TAZ, there was no evidence of study drug related hemorrhage or microhemorrhage in the histopathological examinations performed on tissues. They also noted that:

> "Abnormal platelet function would be expected to increase the overall number of bleeding events throughout different anatomic sites, including sites outside the central nervous system (CNS). As noted in the responses provided to the Agency on 31-Jan-2019 and 15-Mar-2019, bleeding or hemorrhagic events outside the CNS were comparable in frequency between the treatment groups across system organ classes. In addition, the types of bleeding events typically associated with platelet dysfunction, such as

bleeding from mucous membranes and at sites of minor skin trauma (i.e., intravenous line sites) (Casari and Bergmeier 2016), were very rare in PN008."

The Division also consulted the Agency's Division of Hematology Products regarding recommendations to evaluate whether TOL/TAZ causes platelet dysfunction. In the consult response, Dr. Patricia Oneal noted that,

- "…Based on the findings from the hematologists [retained by Merck], it is unclear that the etiology of the intracranial hemorrhages found in the ceftolozane-tazobactam arm was directly the result of aberrations in platelet function…"

- "…The paper by Bower et al (*World Neurosurgery 2018*) describ[es] the biological plausibility of platelet dysfunction as a factor influencing increased bleeding, without thrombocytopenia or increased PT with the use of ceftolozane-tazobactam. The case describes a 53-year old man with hypertension for treatment of an intracranial hemorrhage which occurred after starting empiric piperacillin-tazobactam due to aspiration pneumonia. The platelet function assays (PFAs) were abnormally prolonged from baseline. PFAs trended toward normalization six hours after discontinuation of piperacillin-tazobactam…"

- "…Lastly, ceftolozane/tazobactam is a combination of [a] cephalosporin combined with [a] B-lactamase inhibitor. Some B-lactam antibiotics are reported to produce dose-dependent and duration related effects on the bleeding time and agonist induced platelet aggregation has been found to be reduced in patients receiving piperacillin and other similar antibiotics. The inhibitory effect appears to [be] maximal 1-2 days after administration but can persist for several days after [the] antibiotic [is] withdrawn (Blood 1990). However, the exact mechanism by which β-lactam antibiotics inhibit platelet function is not clear. It has been postulated that the penicillins may impair the interaction of platelet agonists (such as ADP and epinephrine) and/or von Willebrand factor with receptors on platelet surfaces. The clinical relevance of antibiotic induced platelet dysfunction is also not clear and a prolonged bleeding time may not predict clinically significant bleeding…"

CDTL comment: (b) (4) ***I have reviewed the narratives and additional information provided by the Applicant in response to FDA queries for these cases and agree that the observed CNS hemorrhages were most likely related to complications of underlying diseases/co-morbid conditions of these patients and complications of management of the underlying diseases/co-morbid conditions. This safety issue can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with CNS hemorrhage adverse events in the future.***

It should also be noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites.

Hepatotoxicity:
Regarding hepatotoxicity, 11.9% of TOL/TAZ -treated patients and 7.2% of meropenem-treated patients experienced increased hepatic transaminases (adverse reaction terms include: alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hepatic enzyme increased, hypertransaminasemia, liver function test abnormal). Of the subgroup of patients who had normal ALT and AST at baseline, 57% of TOL/TAZ-treated patients and 60% of meropenem-treated patients experienced increases in ALT or AST of greater than 1 to 5 times ULN post-baseline. Additionally, among subjects with abnormal ALT or AST studies at baseline, similar proportions of subjects in both treatment arms experienced increases (or decreases) in ALT and AST based on analysis of maximum shifts from baseline as noted in the review. These proportions of liver enzyme elevations were observed in a HABP/VABP patient population with a high severity of illness. Two TOL/TAZ-treated patients experienced hepatic failure prior to dying; however, they were both severely ill, had multiple chronic medical co-morbidities, and were on multiple medications.

CDTL comment: (b) (4) ***I have reviewed a number of the narratives of patients with adverse events associated with liver enzyme elevations, as well as, additional information provided by the Applicant in response to FDA queries for these cases and have determined that the patients had a number of reasons for elevated liver enzymes (e.g., baseline cirrhosis, hepatic steatosis, sepsis/septic shock, multiple organ failure, cardiac failure/cardiogenic shock, etc.) and it would be difficult to attribute TOL/TAZ exposure as the sole or even most likely etiology for the adverse events. These patients had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20. As noted in the unireview and corroborated in analyses provided by the Applicant, among subjects with normal ALT and AST at baseline, similar numbers of subjects in both treatment arms experienced increases in ALT and AST of greater than 1 to 5 times the upper limit of normal. Two TOL/TAZ-treated patients experienced hepatic failure prior to dying; however, upon review of the narratives and additional information provided for these subjects they were both severely ill, had multiple chronic medical co-morbidities, and were on multiple medications. Therefore, it is unclear how the two hepatic failure events in the TOL/TAZ arm could be attributed to study drug administration with any certainty. This safety issue can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with hepatotoxicity adverse events in the future.***

Nephrotoxicity:
Regarding nephrotoxicity, 8.9% (32/361) of TOL/TAZ-treated patients and 6.1% (22/359) of meropenem-treated patients experienced adverse events potentially associated with nephrotoxicity (adverse reaction terms in the search included: acute renal failure, prerenal failure, renal failure, azotemia, oliguria, anuria). A total of 6 TOL/TAZ-treated patients and one meropenem-treated patient met the pre-specified criteria for withdrawal of study therapy due to the development of end stage renal disease defined as a creatinine clearance of less than 15 mL/min or oliguria (less than 20 mL/h urine output over 24 hours), or if dialysis or hemofiltration was required while the subject was receiving study drug therapy. Renal function recovered or resolved in 11 of the 32 (34%) TOL/TAZ-treated patients and 12 of the 22 (54%) meropenem-treated patients. In 17 of 32 (53%) TOL/TAZ-treated patients and in 6 of 22 (27%) meropenem treated patients, renal function was not recovered/resolved, though it is important to note that many of these patients died. These proportions of renal AEs were observed in a HABP/VABP patient population with a high severity of illness. These renal AEs appeared to be due to progression of the underlying infection, complications related to co-morbidities, or both, and it would be difficult to attribute TOL/TAZ exposure as the sole or even most likely etiology for the adverse events.

As noted in the review, the percentages of subjects with normal creatinine clearance at baseline who then went on to develop mild, moderate, and severe renal impairment was similar between the two treatment arms.

It is also important to note that mortality based on baseline creatinine clearance was similar between the two treatment arms. The following is an excerpt from the Statistical reviewer's Table 19.

Day 28 All-Cause Mortality by Various Subgroups (ITT Population)

	Ceftolozane/Tazobactam	Meropenem	Difference (95% CI)*
Baseline Creatinine Clearance (mL/min)			
≥ 150 (hyperclearance)	10/67 (14.9)	7/64 (10.9)	-4.0 (-15.8, 8.0)
≥ 80 to < 150 (normal)	30/160 (18.8)	38/172 (22.1)	3.3 (-21.1, 27.1)
> 50 to < 80 (mild impairment)	30/82 (36.6)	22/77 (28.6)	-8.0 (-22.0, 6.5)
≥30 to ≤ 50 (moderate impairment)	11/35 (31.4)	10/26 (38.5)	7.0 (-16.0, 30.0)
≥15 to < 30 (severe impairment)	6/17 (35.3)	13/21 (61.9)	26.6 (-4.9, 51.6)
< 15 (ESRD)	-	1/1 (100.0)	NA
>50	70/309 (22.7)	67/313 (21.4)	-1.3 (-8.0, -5.5)
≤ 50	17/52 (32.7)	24/48 (50.0)	17.3 (-3.7, 38.3)

Of note, was a trend toward lower 28-Day all-cause mortality among those patients with baseline creatinine clearance ≤50 mL/min in the TOL/TAZ arm vs. the meropenem arm.

CDTL comment (b) (4) ***have reviewed a number of the narratives of patients with adverse events associated with renal impairment, including but not limited to the subjects who discontinued study therapy due to acute renal failure, as well as, additional information provided by the Applicant in response to FDA queries for these cases and have determined that these patients had multiple reasons for renal impairment and worsening renal function (e.g., sepsis/septic shock, multiple organ failure, cardiac failure/cardiogenic shock, aortic dissection, concomitant administration of nephrotoxic medications, such as vasopressors, etc.) and it would be difficult to attribute TOL/TAZ exposure as the sole or even most likely etiology for the adverse events. These patients had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20. Among subjects with normal creatinine clearance at baseline, similar numbers of subjects in both treatment arms experienced mild, moderate, and severe renal impairment. This safety issue can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with nephrotoxicity adverse events in the future.***

CDTL Assessment:
While I acknowledge the assessment of the clinical reviewer, (b) (4) Based on FDA guidance, to include an adverse event in the Warnings and Precautions section of the label, "…there should be reasonable evidence of a causal association between the drug and the adverse event…" While there were numerical imbalances in some of the subgroups, such a finding is expected with multiple analyses. The patients enrolled in Trial P008 had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20 equating to a predicted mortality rate of 35% or higher.[1] Attribution of these adverse events to study therapy is difficult given the high severity of illness of the patients, their underlying infections and other critical illnesses, complications related to co-morbid conditions, and multiple concomitant medications.

With particular regard to the observed intracranial hemorrhage adverse events, it is also noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites. Additionally, there is no evidence from the literature that TOL/TAZ causes platelet dysfunction.

[1] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

These safety issues can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with these adverse events. Additionally, patients with HABP/VABP are typically closely monitored, often in an intensive care unit, and any decrement in renal or hepatic function can be detected.

Division Director Comment:

I agree with the assessment by Dr. Allende and Dr. Kim, that the Applicant has provided substantial evidence of the effectiveness of ceftolozane-tazobactam for the treatment of HABP/VABP due to susceptible designated organisms. I also agree with their assessment that there was a numerical imbalance in some reported adverse events. I agree with Dr. Kim's assessment that these safety findings can be adequately addressed in the Adverse Reactions section of the package insert (b) (4)

1.4. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In this sNDA, the Applicant is seeking an indication for the treatment of HABP/VABP. In support of this indication, the Applicant has provided data from a Phase 3 noninferiority trial in patients with HABP/VABP where TOL/TAZ was compared to meropenem. The study met its primary endpoint by demonstrating that TOL/TAZ was noninferior to meropenem for the primary endpoint of Day 28 all-cause mortality in the ITT population: Day 28 all-cause mortality rate was 24.0% in the TOL/TAZ group versus 25.3% in the meropenem group for a treatment difference (stratified 2-sided 95% CI) of 1.1% (-5.1, 7.4%). The key secondary endpoint, clinical cure, supported the finding of noninferiority. The clinical cure rate at the TOC visit was 54.4% in the TOL/TAZ group versus 53.3% in the meropenem group. The overall treatment difference (stratified 2-sided 95% CI) was 1.1% (-6.2, 8.3%). This single adequate and well-controlled trial provided substantial evidence of effectiveness as the product is already approved for the treatment of cUTI and cIAI. Additional supportive information was provided from in vitro studies and animal models of infection.

The most common adverse events (greater than or equal to 2% incidence) experienced by patients in this trial were: elevation in hepatic transaminases, nephrotoxicity (renal impairment/renal failure), diarrhea, intracranial hemorrhage, vomiting, pyrexia, and *Clostridium difficile* colitis. The safety profile in this severely ill patient population was characterized by high rates of fatal and serious adverse events in both arms, with some numerical imbalances with respect to certain adverse events such as intracranial hemorrhage, nephrotoxicity, and elevation in hepatic transaminases. The lack of a second study to assess the reproducibility of these findings is a limitation to the safety and causality assessment. The higher incidence of these adverse events in the treatment arm will be communicated in labeling and monitored postmarketing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The HABP/VABP patient population is characterized by comorbid conditions of respiratory failure, sepsis, multi-organ failure which may include nervous, renal, hepatic and circulatory systems. There is a significant risk of death. • Gram-negative pathogens can account for >60% of isolated bacteria in HABP/VABP, with one of the most frequently isolated pathogens being *Pseudomonas aeruginosa*. • *P. aeruginosa* has been associated with one of the highest mortality rates among Gram-negative pathogens (approximately 35-40%).	HABP and VABP are serious and life-threatening infections and are frequently caused by Gram-negative pathogens with resistance to multiple classes of existing antibacterial drugs. Multi-drug resistant Gram-negative pathogens have been associated with increased incidence of treatment failure and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Other common Gram-negative pathogens isolated in patients with HABP and VABP are *Escherichia coli, Klebsiella pneumoniae, Enterobacter spp. and Acinetobacter spp.*	
Current Treatment Options	• Treatment options for HABP/VABP are limited but may include carbapenems, such as meropenem and imipenem; β-lactam/β-lactamase inhibitor combinations such as ceftazidime/avibactam and piperacillin/tazobactam, cephalosporins, such as cefepime and ceftazidime, fluoroquinolones, and aminoglycosides. Polymyxins and tetracyclines may be used when no other options are available.	There are limited treatment options for HABP/VABP due to resistant organisms. The existing drugs are expected to decline in utility over time due to the emergence and spread of resistant Gram-negative pathogens. The availability of beta-lactams combined with beta-lactam inhibitor combinations against resistant Gram-negative pathogens can potentially help reduce carbapenem utilization.
Benefit	• In this Phase 3 HABP/VABP trial, the 28-day all-cause mortality rate in the ITT population was 24.0% in the TOL/TAZ arm versus 25.3% in the meropenem group for a treatment difference (stratified 2-sided 95% CI) of 1.1% (-5.1, 7.4%) (the primary endpoint). • The clinical cure rate at the TOC visit was 54.4% in the ceftolozane/tazobactam group versus 53.3% in the meropenem group. The overall treatment difference (stratified 2-sided 95% CI) was 1.1% (-6.2, 8.3%) (secondary endpoint). • Resistance to certain Enterobacteriaceae is an area where more targeted therapeutic options are needed to avoid excessive use of carbapenems and the adverse consequences of that use on emergence of resistance.	TOL/TAZ was noninferior to meropenem in the treatment of patients with HABP/VABP. The secondary endpoint of clinical cure supported the finding of non-inferiority.
Risk and Risk Management	• Key safety concerns for TOL/TAZ include a higher number of reports of intracranial hemorrhages, including those with fatal outcomes, elevation in transaminases and renal impairment, *C. difficile* associated diarrhea, and hypersensitivity, of which these last two are warnings already in the current label.	The benefits and risks of TOL/TAZ are communicated in labeling. Monitoring for adverse events of special interest will continue in the post-marketing phase. No other risk mitigation strategies are needed at this time.

1.5. Patient Experience Data

Patient experience data were not submitted in this application, are not available, and are not applicable to the study endpoints and indication.

2 Therapeutic Context

2.1. Analysis of Condition

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are acute infections of the pulmonary parenchyma associated with clinical signs and symptoms and chest radiographic findings occurring in a patient after being hospitalized. These two conditions are caused by a variety of Gram-positive and Gram-negative bacteria and are serious, life-threatening infections. The Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines distinguish the following types of pneumonia:

Hospital-acquired (bacterial) pneumonia (HAP) (HABP for the purposes of this review): pneumonia not incubating at time of hospital admission, occurring 48 hours or more after admission, and not associated with mechanical ventilation.

Ventilator-associated (bacterial) pneumonia (VAP) (VABP for the purposes of this review): pneumonia occurring more than 48 hours after endotracheal intubation (Kalil et al. 2016).

In hospitalized patients with pneumonia, Gram-negative organisms can account for >60% of isolated bacteria, with one of the most frequently isolated pathogens being *Pseudomonas aeruginosa*. *P. aeruginosa* has been associated with one of the highest mortality rates among Gram-negative pathogens (approximately 35-40%)(Lambert et al. 2011). Other common Gram-negative pathogens isolated in patients with either HABP or VABP are *Escherichia coli, Klebsiella pneumoniae, Enterobacter spp. and Acinetobacter spp.* Drug resistance is common: according to the CDC's National Healthcare Safety Network in the years 2009-2010, approximately 50% of *S. aureus* isolates are methicillin-resistant, 25% to 30% of Pseudomonas and Klebsiella isolates are ceftazidime and cefepime resistant, and 60% of Acinetobacter isolates are carbapenem resistant (Sievert et al. 2013). Risk factors for drug-resistant bacteria include severity of illness, prolonged mechanical ventilation, recent broad-spectrum antimicrobial exposure, recent hospitalization or residence in an extended care facility, and immunosuppression. Studies on whether or not drug-resistant pathogens increase attributable morbidity and mortality are inconsistent (Rello et al. 1994; Vidaur et al. 2008; Damas et al. 2011).

Despite high absolute mortality rates in HABP/VABP patients, the mortality attributable to the infection is difficult to gauge. Many studies have found that HABP and VABP are associated with 20 to 50% risk of death (Kalil et al. 2016). However, many of these critically ill patients die from their underlying diseases and not from pneumonia.

2.2. Analysis of Current Treatment Options

The initial treatment of HABP/VABP is empiric. Treatment regimens are guided by the patient's risk factors, and knowledge of the local epidemiology of likely infecting organisms and their

antibacterial susceptibility patterns. Empiric treatment of HABP or VABP usually includes coverage of *S. aureus*, *Pseudomonas aeruginosa* and other Gram-negative bacilli. Combinations of antimicrobials are frequently used. Definitive treatment follows based on the diagnostic workup and the patient's status and response to empiric treatment.

Table 1. Currently Available Treatments for Gram Negative HABP/VABP

Product Class	Product (s) Name	Relevant Indication	Year of Initial Approval	Dosing/ Administration*	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments (for HABP/VABP and/or lower respiratory infections (LRTI) including pneumonia in a hospital setting)						
β-lactam/β-lactamase inhibitor combination	Ceftazidime/ avibactam	HABP/VABP	2018	2.5g IV Q 8h, 7 to 14 days	Hypersensitivity reactions, hematologic (thrombocytopenia, anemia), liver enzyme elevations, renal toxicity, *C. difficile* associated diarrhea (CDAD)	Used empirically in combination with aminoglycosides or a quinolone in high risk patients and high likelihood of multi-drug resistant organisms, then monotherapy as per antibacterial susceptibility
	Piperacillin/ tazobactam	Nosocomial pneumonia	1993	4.5g IV Q 6 h, 7 to 14 days		
Cephalosporins: 2nd, 3rd, and 4th generations	Cefotetan	LRTI	1985	2 to 3 g IV Q 12hs		
	Cefoxitin	LRTI	1978	1g to 2g IV Q6-8h		
	Cefuroxime	LRTI	1986	750mg to 1.5g Q 8h		
	Cefotaxime	LRTI	1981	1-2 g IV Q 8h		
	Ceftazidime	LRTI	1985	2g IV Q 8h/7days		
	Ceftriaxone	LRTI	1984	1-2 g IV QD		
	Cefepime	Pneumonia (moderate to severe)	1996	1-2 g IV Q8-12h		
Fluoroquinolones	Levofloxacin	Nosocomial pneumonia	1996	750 mg Q 24h, 7 to 14 days	Prolonged QTC, tendon rupture/tendonitis, CNS effects and peripheral neuropathy	Commonly used in combination with B-lactams
	Ciprofloxacin	Nosocomial pneumonia	1990	400 mg IV Q8h, 10 to 14 days		
Carbapenems	Imipenem-cilastatin	LRTI	1985	500 mg IV Q6 or 1000 mg IV Q8h	Hypersensitivity, seizures, CDAD	Use according to local susceptibility
Monobactams	Aztreonam	LRTI	1986	1 to 2g IV Q 8-12h	Hypersensitivity, CDAD	Rarely used as monotherapy
Aminoglycosides	Gentamicin	LRTI	1981	3 to 5 mg IV Q8h	Auditory/vestibular, renal, NM blockade	In combination with β-lactams or fluoroquinolones
	Amikacin	LRTI	1986	7.5 mg IV Q12h		
	Tobramycin	LRTI	1981	1 mg IV Q8h		
Tetracyclines	Tigecycline	CABP±	2005	50 mg IV Q12h		1% higher mortality in ventilated patients¥

Product Class	Product (s) Name	Relevant Indication	Year of Initial Approval	Dosing/ Administration*	Important Safety and Tolerability Issues	Other Comments
Other Treatments (recommended by IDSA/ATS guidelines[Ω] but not FDA approved for specific respiratory infections)						
Carbapenems	Meropenem	cIAI, SSSI and meningitis	1996	1g IV Q8h	Hypersensitivity, seizures, CDAD	Usually reserved for more severe illness, high risk of multi-drug resistant organisms and empiric treatment when these are suspected.
	Doripenem	cUTI and cIAI	2007	500mg IV Q8h	Increased risk of death for VABP vs. imipenem[∞]	
Polymyxins	Polymyxin B	UTIs, meninges, bloodstream and eye infections	1970	15,000u/kg IV Q12h	Renal and neurotoxicity	
	Colistimethate sodium	Acute or chronic infections due to sensitive bacteria	1970	2.5 to 5 mg/kg in 4 daily doses	Renal and neurotoxicity	

* Unadjusted for renal function
[±] Community-acquired bacterial pneumonia
[¥] (FDA Drug Safety Communication 2010)
[Ω] (American Thoracic Society and Infectious Diseases Society of America 2005; FDA Drug Safety Communication 2010)
[∞] (FDA Drug Safety Communication 2010; Kollef et al. 2012)
SSSI= Skin and Skin Structure Infections

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Zerbaxa was approved in the United States on December 19, 2014 (NDA 206829), for the treatment of cIAI (in combination with metronidazole) and cUTI (including pyelonephritis) at a dose of 1.5 g (1 g ceftolozane and 0.5 g tazobactam), administered q8h by IV infusion over 1 hour in patients 18 years or older. Cubist Pharmaceuticals LLC, a subsidiary of Merck & Co., Inc, is the Applicant.

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory communications and milestones in the development of ceftolozane/tazobactam for HABP/VABP:

- 12 MAR 2012 - Type C Meeting: Agreement on a single pivotal study for HABP/VABP, provided that evidence of efficacy is demonstrated, along with acceptable drug penetration into extracellular lung fluid (ELF). Recommendation to Applicant to include patients with drug-susceptible pathogens and enrich enrollment of patients at highest risk for multi-drug resistant (MDR) Gram-negative pathogens and to add a Data Safety Monitoring Board (DSMB) with an interim safety analysis to enhance safety assessment of the higher dose used in this indication.
- 20 FEB 2013 - QIDP designation for HABP/VABP granted
- 26 APR 2013 – Fast Track designation for HABP/VABP granted
- 20 AUG 2013 – The Division recommended that the Applicant conduct a trial in HABP/VABP that includes both drug-susceptible and multi-drug resistant (MDR) pathogens, in response to Applicant's proposal to conduct the HABP/VABP study only in patients with *P. aeruginosa* infections. Such a trial would enroll all-comers to establish noninferiority (NI) for a mortality endpoint, and if NI is demonstrated, superiority could be evaluated in patients with resistant pathogens.
- Study endpoints, comparator, eligibility criteria and size of the safety database (approximately 300 subjects) were agreed upon.
- 16 JAN 2015 – First patient enrolled in the Phase 3 study
- 30 APR 2018 – Type C Meeting: Advice to Applicant to have a separate set of susceptibility breakpoints for the HABP/VABP indication, if supported by data from the 3 g Q8 hours dose
- 06 JUN 2018 – Last patient enrolled has last study visit in the trial
- 27 JUL 2018 – Database lock date for the Phase 3 study

- 17 OCT 2018 – Pre-NDA Meeting: Applicant provided preliminary data from the Phase 3 study (PN008). The Division provided recommendations on the format and content of the proposed sNDA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Aisha Johnson, MD, MPH, MBA, from the Good Clinical Practice Assessment Branch/Division of Clinical Compliance Evaluation/OSI composed the Clinical Inspection Summary. Briefly, two study sites (Drs. Ülo Kivistik and Jiri Vyhnal) were selected for clinical inspection. The study data derived from these two clinical sites, based on the inspections, were considered reliable in support of the proposed indication. The final compliance classification for both sites was "no action indicated" (NAI).

4.2. Product Quality

No new product quality information was submitted with the sNDA.

4.3. Clinical Microbiology

The Applicant has proposed (b) (4) An evaluation of the Applicant's proposal from the Agency's clinical microbiology perspective is below. The following recommendations were made to subsection 12.4 the labeling:

- (b) (4)
- Disk breakpoints were re-evaluated by the Applicant for Enterobacteriaceae and accepted by the Agency as having the lowest possible minor error rate.
- (b) (4)
- (b) (4)
- Information pertaining to each organism in the resistance section was grouped together for clarity.
- (b) (4)
- *S. marcescens* (b) (4) is in the first list under the HABP/VABP indication.
- (b) (4)

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical study information was included with this sNDA. However, in Section 13.1 of the product label included with the supplement, a new genetic toxicology study for ceftolozane was listed. The Applicant submitted the study report for this study [Study No.: TT #16-9019: In Vitro Mammalian Cell Forward Gene Mutation (CHO/HPRT) Assay with Duplicate Cultures] to the NDA 206829/S-008 supplement application on 3/27/2019 in response to an information request. A summary review and evaluation of the new genetic toxicology study is described in Section 5.2.1.

5.2. Toxicology

5.2.1. Genetic Toxicology

In Vitro Assays in Mammalian Cells

Study title/ number: In Vitro Mammalian Cell Forward Gene Mutation (CHO/HPRT) Assay with Duplicate Cultures/ Study No.: TT #16-9019

Key Study Findings:

- Ceftolozane sulfate was shown to be negative for mutagenicity at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells in the presence and absence of S9 metabolic activation.
- Positive control agents (ethyl methanesulfonate and benzo(a)pyrene) significantly increased mutant frequencies in the absence and presence of S9 activation compared to control values confirming the sensitivity of the test system.

GLP compliance: Yes

Test system: The test system was the CHO-K1-BH4 cell line. Cell cultures were incubated with five concentrations of ceftolozane sulfate (31.3, 62.5, 125, 250, and 500 mcg/ml) with and without S9 activation, then assessed for mutant frequencies.

Study is valid: Yes, all the criteria for determination of a valid test were satisfied.

6 Clinical Pharmacology

Executive Summary

The Office of Clinical Pharmacology reviewed the information contained in NDA206829, S-008. The clinical pharmacology information provided in this supplemental NDA supports the approval of Zerbaxa for the treatment of HABP/VABP in patients 18 years of age and older. See Table 2 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 2. Summary of OCP's Recommendations and Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Phase 3 clinical trial (Study P008) in HABP/VABP patients treated with 3 g of Zerbaxa (ceftolozane 2 g and tazobactam 1 g) every 8 hours demonstrated noninferiority to meropenem 1 g every 8 hours for the primary endpoint, 28-day all-cause mortality.
General dosing instructions	The recommended dosing regimen for HABP/VABP is 3 g administered every 8 hours by intravenous infusion for over 1 hour in patients 18 years of age or older with creatinine clearance (CLcr) >50 mL/min. The recommended treatment duration is 8 to 14 days for HABP/VABP. The treatment duration should be guided by the severity of infection and the patient's clinical and bacteriological progress.
Dosing in subgroup (intrinsic/extrinsic)	The following Zerbaxa dosage regimen is recommended for patients with CLcr ≤50 mL/min. **Estimated CLcr (mL/min)*** / **Zerbaxa dosage regimen for patients with HABP/VABP†** 30 to 50 — 1.5 g (1 g and 0.5 g) intravenously every 8 hours 15 to 29 — 750 mg (500 mg and 250 mg) intravenously every 8 hours End-stage renal disease (ESRD) on hemodialysis (HD) — 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 treatment period (on HD days, administer the dose at the earliest possible time following completion of dialysis) † (b) (4) * CLcr estimated using Cockcroft-Gault Equation
Labeling	The Applicant's proposed labeling is generally acceptable. However, the review team has specific recommendations to change content and format.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant has conducted four (three new studies for this indication and one study from previous application) clinical studies that evaluated the pharmacokinetics (PK) of ceftolozane-tazobactam 3 g every 8 hours: Study P007 (Phase 1), Study P018 (Phase 1), Study P028 (Phase 1), and Study P008 (Phase 3). Study P028 was submitted with the original application. Detailed

PK information comparing healthy subjects and patients with HABP/VABP are presented in Section 6.3.1.

Overall, the PK properties of ceftolozane and tazobactam in HABP/VABP patients are comparable to those in cIAI and cUTI patients. However, the dose-normalized AUC and C_{max} of ceftolozane and tazobactam are substantially different between the patient groups (see Section 6.3.1). Their differences are addressed in the population PK models for HABP/VABP patients.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed ceftolozane-tazobactam dosing regimen of 3 g (2 g ceftolozane and 1 g tazobactam) administered every 8 hours as a 1-hour IV infusion in patients 18 years of age or older with CLcr >50 mL/min was acceptable based on the results of the probability of pharmacokinetic-pharmacodynamic (PK-PD) target attainment (PTA) analysis as well as clinical efficacy demonstrated in Study P008.

The proposed treatment duration is for up to 14 days, which would be guided by the severity of infection and patient's clinical and bacteriological status.

Therapeutic Individualization

Therapeutic individualization was not proposed, but the dosing regimen should be adjusted based on the renal function (i.e., CLcr). The Applicant's proposed dose adjustments of ceftolozane-tazobactam for patients with CLcr ≤50 mL/min, including patients with ESRD on HD, were acceptable. For further details, see Section 6.3.2.

Outstanding Issues

None

Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 3. Pharmacology Information

General Information	
Drug Exposure Following the Therapeutic Dosing Regimen	**Plasma Exposure** Post-hoc population PK model predicted ceftolozane and tazobactam plasma PK parameters (geometric mean [GMCV%]) following IV administration of 3 g every 8 hours for 8 to 14 days in patients 18 years of age or older with HABP/VABP (Study P008) are reported below. **Plasma PK Parameter (N=247)** / **HABP/VABP Ceftolozane** / **Tazobactam** AUC_{0-8} (µg·h/ml) / 341 (55.2) / 56.1 (76.4) C_{max} (µg/ml) / 96.1 (43.3) / 24.2 (41.6)
Healthy *vs.* Patients	The ceftolozane geometric mean (GM) plasma AUC_{0-8} is similar between HABP/VABP infected patients and healthy subjects; however, the tazobactam GM plasma AUC_{0-8} is 25% higher in the HABP/VABP patients than in healthy subjects. The GM C_{max} of both ceftolozane and tazobactam are 25-30% lower in HABP/VABP patients *vs.* healthy subjects.
Variability	In HABP/VABP, ceftolozane and tazobactam AUC_{0-8} CV%: 60.2% and 104%, respectively, and C_{max} CV% was 44.2% and 48.8%, respectively. In healthy subjects, ceftolozane and tazobactam AUC_{0-8} CV%: 13.8% and 14.5%, respectively, and C_{max} CV% was 12.5% and 11.5%, respectively.
Accumulation	The GM plasma accumulation of ceftolozane and tazobactam was not substantial (≤1.45) in HABP/VABP patients with CLcr >50 mL/min. However, the accumulation of ceftolozane increased to ~2.1 and 2.6 in patients with CLcr of 30-50 mL/min and 15-29 mL/min, respectively. Similar to ceftolozane, the accumulation ratio of tazobactam increased from ≤1.18 in HABP/VABP patients with CLcr >50 mL/min to ~1.5 and 2.0 in patients with CLcr of 30-50 mL/min and 15-29 mL/min, respectively.
T_{max}	The ELF concentrations of ceftolozane and tazobactam are predicted to reach maximum at ~6 and 2 hours after administration, respectively.
Volume of Distribution	GM V_{ss} of ceftolozane and tazobactam in HABP/VABP patients was 25.8 L and 42.0 L, respectively.
Protein Binding	Ceftolozane protein binding in plasma is ~16-21%. The plasma protein binding of tazobactam is known to be ~30%.
Elimination	
Half-life	GM half-life of ceftolozane and tazobactam in patients with HABP/VABP was 3.48 and 2.89 hours, respectively.
Metabolism	Ceftolozane is minimally metabolized. Less than 20% of tazobactam is metabolized to the inactive metabolite, tazobactam M-1.
Excretion	Ceftolozane is entirely excreted unchanged in urine. Tazobactam is primarily (~80%) excreted as unchanged drug in the urine. Tazobactam M-1 is excreted by the kidneys.

Since the PK of ceftolozane and tazobactam are dose-proportional, this information was used to evaluate the potential differences in PK parameters due to infection type. The cIAI/cUTI patient dosing regimen (1.5 g every 8 hours) was dose-normalized and the PK parameters were

compared to the HABP/VABP patient dosing regimen (3 g every 8 hours). The dose-normalized GM AUC_{0-8} value of ceftolozane for HABP/VABP patients were comparable to GM AUC_{0-8} exposures in patients with cIAI and cUTI (<20% difference). The dose-normalized ceftolozane GM C_{max} for patients with cIAI, cUTI and cIAI/cUTI combined were ~12%, 47% and 28% higher, respectively, than that for patients with HABP/VABP. Similarly, the dose-normalized tazobactam GM AUC_{0-8} were comparable between cUTI/CIAI patients and HABP/VABP patients while the dose-normalized tazobactam GM C_{max} values for patients with cIAI, cUTI and cIAI/cUTI combined were ~27%, 64%, and 39% higher, respectively, compared with that for patients with HABP/VABP.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of Zerbaxa in patients with HABP and VABP was provided by Study P008. Ceftolozane-tazobactam demonstrated noninferiority to meropenem for the primary endpoint (28-day all-cause mortality) with supportive findings for the secondary endpoint of clinical cure rate at the TOC visit, as the lower bound of the 2-sided 95% CI around the treatment difference was greater than -10% (for 28-day mortality) and -12.5% (for clinical cure at TOC) in the ITT population. Refer to Section 8.1 "Review of Relevant Individual Trials Used to Support Efficacy" for details on the study design and efficacy evaluation. Additionally, the results of the PTA analysis (i.e., the PK-PD target attainment in >90% of patients) support the effectiveness of ceftolozane-tazobactam in HABP/VABP patients (see below and Section 15.4.2 for further detail).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the Applicant's proposed dosing regimen of 3 g (2 g ceftolozane and 1 g tazobactam) every 8 hours is acceptable for the general patient population 18 years of age or older with HABP/VABP.

(b) (4)

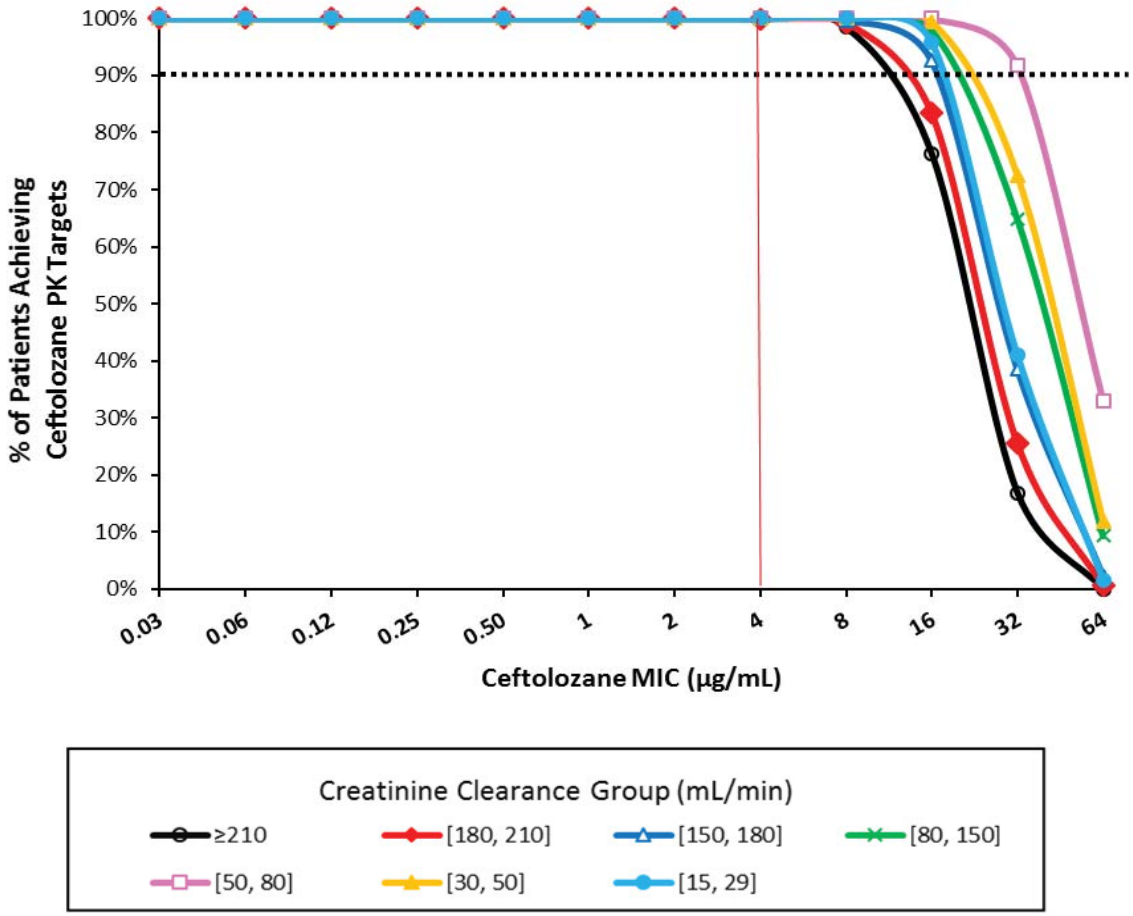
Since the lung penetration, relative to the plasma, was ~50% and 62% for ceftolozane and tazobactam, respectively, the dosing regimen was increased 2-fold. To support the 3 g every 8-hour dosing regimen, a PTA analysis was conducted. Using a population PK model developed with plasma concentration data and lung penetration data from healthy subjects and HABP/VABP (confirmed or suspected) patients, combined with PK-PD targets associated with efficacy derived from a murine thigh infection model, Monte Carlo simulations were conducted to determine the PTA in HABP/VABP patients receiving the proposed dosing regimen.

Probability of Pharmacokinetic-Pharmacodynamic Target Attainment Analysis

The Applicant refined a previously-developed population PK models with plasma data from 3 Phase 3 studies. With the refined population PK models, Monte Carlo simulation were conducted to generate plasma and ELF concentration-time profiles in 1000 virtual HABP/VABP patients per renal function group (separated by CLcr). The PK-PD targets for efficacy were determined using a murine thigh infection model. The PTA analyses were conducted with the simulated plasma and ELF concentration-time profiles and the PK-PD targets.

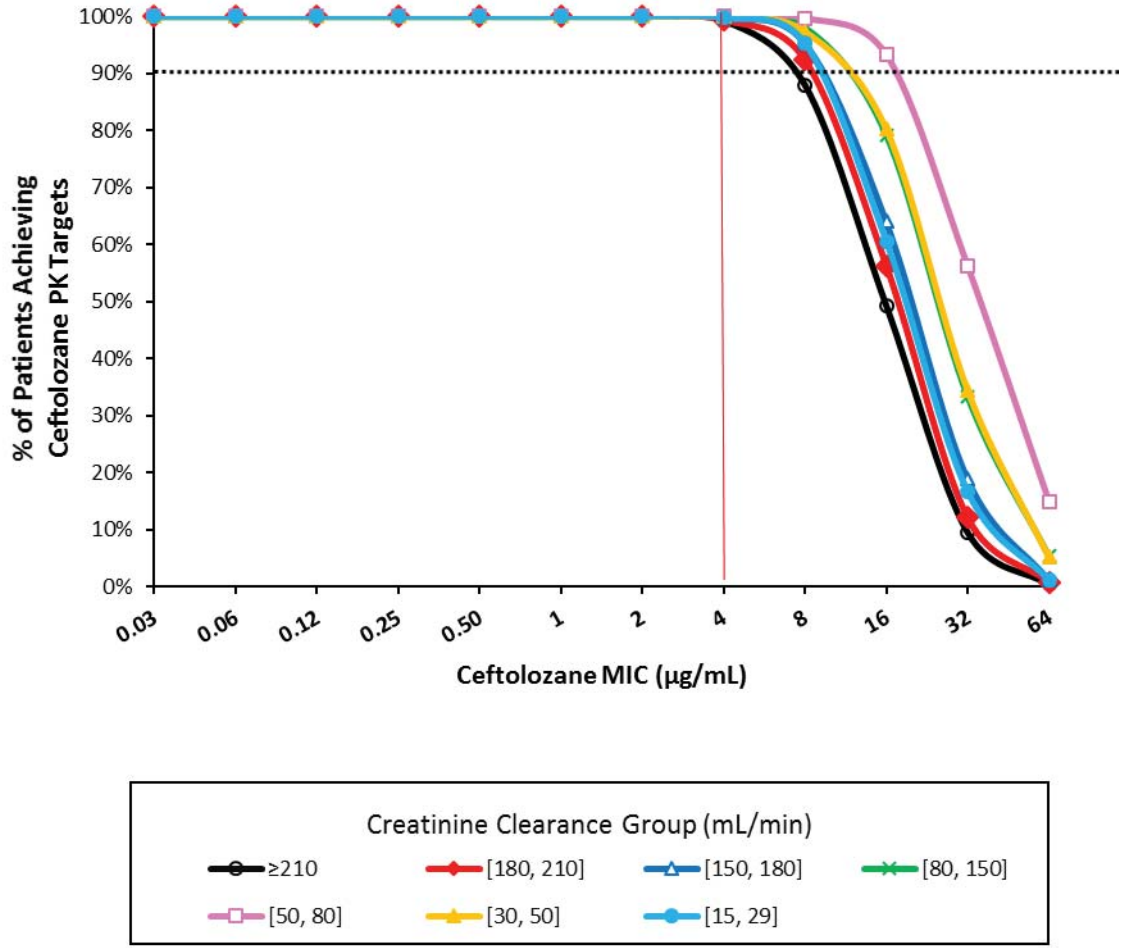
The ceftolozane PK-PD target for efficacy is 40% of a dosing interval that the free drug concentration exceeds the minimum inhibitory concentration of the infecting organism (40% *f*T>MIC). The PK-PD target corresponds with a conservative 2-$\log_{10}$ bacterial density reduction from a 0-hour baseline. The tazobactam PK-PD target for HABP/VABP was the same target that was used for cUTI and cIAI, 20% of a dosing interval that the free drug concentration remained above the threshold concentration of 1 µg/mL (20% *f*T>C_T). This tazobactam PK-PD target appears to be reasonable because the tazobactam exposure required to inhibit beta-lactamase may not be related to indications. The increase in dosing regimen to 3 g every 8-hour ceftolozane-tazobactam for HABP/VABP was not due to a change in PK-PD target for efficacy, as the MIC values reached were similar for the PK-PD targets for 1-log and 2-log bacterial reduction. As shown in Figure 1 and Figure 2, the dosing regimen proposed by the Applicant produces an exposure of ceftolozane in both plasma and ELF required to reach the PK-PD target in >90% patients at the *Pseudomonas aeruginosa* in vitro susceptibility testing interpretation criteria or breakpoint for ceftolozane-tazobactam of 4 µg/ml in patients 18 years of age or older with HABP/VABP. For further details of the PTA analysis, see Section 15.4.2. For tazobactam, the PK-PD target of 20% *f*T>C_T = 1 µg/mL was achieved in >90% of patients with CLcr values ≥ 15 mL/min for plasma, and in ≥87% of patients with CLcr values ≥ 30 mL/min for ELF (Table 5).

Figure 1. Percent of Patients with Different Creatinine Clearance Values Achieving 40% *f*T>MIC for Ceftolozane in Plasma at Steady State using Non-Clinical PK-PD Targets for Efficacy



The solid red vertical line represents *Pseudomonas aeruginosa* in vitro breakpoint for ceftolozane. The dotted black horizontal line represents 90% probability of PK/PD target attainment.

Figure 2. Percent of Patients with Different Creatinine Clearance Values Achieving 40% *f*T>MIC for Ceftolozane in Epithelial Lining Fluid at Steady State using Non-Clinical PK-PD Targets for Efficacy



The solid red vertical line represents *Pseudomonas aeruginosa* in vitro breakpoint for ceftolozane. The dotted black horizontal line represents 90% probability of PK/PD target attainment.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes, an alternative dosing regimen is required in patients with CLcr ≤50 mL/min, as ceftolozane-tazobactam is extensively eliminated by the kidneys via the glomerular filtration. Patients with renal impairment were shown to have an increased ceftolozane-tazobactam exposures of ~1.25, ~2-to-2.5 and ~4-to-5-fold increase at CLcr of 50-80, 30-50 and 15-29 mL/min, respectively, compared to patients with CLcr of >80 mL/min. A 2-to-3-fold higher exposure was observed in patients (b) (4) on HD when compared to patients with CLcr 15-30 mL/min. Therefore, dose adjustments in patients with CLcr ≤50 mL/min are warranted, as described in the current ceftolozane-tazobactam label for the cUTI and cIAI indication.

Dosing in patients with CLcr ≥15 to 50 mL/min

Patients with CLcr of 30-50 mL/min and 15-29 mL/min were dosed at 1.5 g every 8 hours and 0.75 g every 8 hours, respectively. The CLcr categories are the same as the original indications (i.e., cUTI and cIAI), but the ceftolozane-tazobactam dosing regimens are 2-fold higher than those approved for cIAI and cUTI. The ceftolozane PTA at the dosing regimens selected for Study P008 in patients with renal impairment exceeded 90% in plasma and ELF for Gram-negative bacteria with ceftolozane MICs of 16 and 8 µg/mL, respectively (Table 4). The PTA of steady-state tazobactam in plasma and ELF were >90% for all virtual patient groups except ELF in patients with CLcr of 15-29 mL/min (87%) (Table 5).

When comparing the simulated ceftolozane exposure measures across renal function groups, the ceftolozane and tazobactam AUC_{0-8} and C_{max} for patients with CLcr ≥15 to 50 mL/min were comparable to or lower than those for patients with CLcr 80-150 mL/min (Table 6). Thus, minimal dose-related safety concerns can be deduced from the ceftolozane-tazobactam AUC_{0-8} and C_{max} exposure measures for patients with CLcr ≥15 to 50 mL/min.

Table 4. Probability of HABP/VABP Patients with Different Creatinine Clearance Values Achieving 40% *f*T>MIC for Ceftolozane in Plasma and ELF at Steady State

MIC (µg/mL)	40% *f*T>MIC 4		8		16	
	Plasma	ELF	Plasma	ELF	Plasma	ELF
CLcr (mL/min)						
15-29	1	1	1	0.95	0.96	0.61
30-50	1	1	1	0.97	0.99	0.80
50-79	1	1	1	1	1	0.93
80-149	1	1	1	0.98	0.98	0.79
150-179	1	1	1	0.95	0.93	0.64
180-209	1	0.99	0.99	0.92	0.83	0.56
≥210	1	0.99	0.99	0.88	0.76	0.49

Table 5. Probability of HABP/VABP Patients with Different Creatinine Clearance Values Achieving 20% *f*T>C_T = 1 µg/mL for Tazobactam in Plasma and ELF at Steady State

	20% *f*T>C_T=1 µg/mL	
	Plasma	ELF
CLcr (mL/min)		
15-29	1	0.87
30-50	1	0.96
50-79	1	0.99
80-149	1	0.98
150-179	1	0.94
180-209	0.99	0.92
≥210	0.98	0.92

Table 6. Simulated Mean Plasma AUC and C_{max} for Both Ceftolozane and Tazobactam at Steady State Across Different Levels of Renal Function

Renal Function (mL/min)	80-150[a]	50-80[a]	30-50[b]	15-29[c]	<15 on HD (Day 7)[d]	<15 on HD (Day 14)[d]
Ceftolozane AUC_{0-8} (µg·h/mL)	410	576	426	310	543	654
C_{max} (µg/mL)	109	132	84.3	53.8	87.8	90.3
Tazobactam AUC_{0-8} (µg·h/mL)	66.2	88.1	59.4	45.8	58.8	63.9
C_{max} (µg/mL)	26.1	30.4	17.5	10.9	11.7	11.7

HD = hemodialysis
[a] 3 g (2 g ceftolozane + 1 g tazobactam) every 8 hours
[b] 1.5 g (1 g ceftolozane + 0.5 g tazobactam) every 8 hours
[c] 0.75 g (0.5 g ceftolozane + 0.25 g tazobactam) every 8 hours
[d] 2.25 g (1.5 g ceftolozane + 0.75 g tazobactam) loading dose, then 0.45 g (0.3 g ceftolozane + 0.15 g tazobactam) every 8 hours

Dosing in patients with CLcr (b) (4) (ESRD on HD):

In patients with ESRD on HD, the Applicant proposed a one-time 2.25 g loading dose, then a 0.45 g every 8-hour maintenance dose for a 14-day treatment duration of HABP/VABP. The proposed loading and maintenance dose are 3-fold higher than the approved dosing regimen used for cIAI and cUTI indication. The Applicant proposed a 3-fold higher dosing regimen after they found that the 2-fold higher dosing regimen (1.5 g loading, then 0.3 g every 8-hour maintenance) would not be sufficient to achieve a joint PTAs of >90% in patients with ESRD on HD, and the 3-fold higher dosing regimen would nearly achieve a joint PTA of 90% in ELF as well as in plasma (see Section 15.4.2 for further detailed discussion). Briefly, PK differences in both ceftolozane and tazobactam were observed in ESRD patients when compared to non-ESRD patients. The ceftolozane influx rate constant from plasma to the ELF was predicted to be low, resulting in a low initial ceftolozane lung penetration and PTA <90% on day 1; however, the low rate of elimination from ELF led to a sustained lung exposure resulting in a ceftolozane lung PTA >90% from day 2 to day 7. The tazobactam influx rate constant from plasma to the ELF was predicted to be high, resulting in a tazobactam lung PTA >90% on day 1; however, the high rate of elimination from ELF, coupled with ~66% drug removal by HD, resulted in tazobactam PTA <90% in ELF from days 2 to 7.

When comparing the simulated ceftolozane AUC_{0-8} across renal function groups, as shown in Table 6, the ceftolozane AUC_{0-8} and C_{max} exposures for patients with ESRD were ~60% higher and ~17% lower, respectively, than the 80-150 mL/min renal group. Meanwhile, tazobactam AUC_{0-8} and C_{max} for patients with ESRD were similar to and ~55% lower than, respectively, for patients with CLcr 80-150 mL/min. Collectively, the proposed dosing regimen for patients (b) (4) on HD would be effective without any safety concerns.

Dosing in patients with augmented renal function (ARF):

Patients with ARF were evaluated in Study P007 and Study P008. The simulated GM plasma and ELF AUC_{0-8} exposures in patients with ARF were lower in both ceftolozane (~21 to 38%) and tazobactam (~24 to 37%) than in patients with CLcr 80-150 mL/min. Despite the PK differences between patients with ARF and normal renal function, the joint PTAs of patients with ARF (CLcr 150-210 mL/min) were >90% at MIC of up to 8 µg/mL in both plasma and ELF. In patients with CLcr >210 mL/min, the PTAs were >90% in both plasma and ELF at MIC of up to 4 µg/mL. Thus, patients with ARF do not appear to need a dose adjustment from the 3 g every 8-hour dosing regimen in patients with CLcr >50 mL/min. Note that in Study P008, the efficacy in 60 patients with CLcr >150 mL/min in the ceftolozane-tazobactam arm were similar to that in patients of the control arm treated with meropenem as well as in non-ARC patients of the ceftolozane-tazobactam arm (see Section 8.1.2).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No new drug-drug interaction studies were performed specific to support the HABP/VABP indication. Based on the original indication, ceftolozane-tazobactam is unlikely to cause clinically relevant drug-drug interactions relevant to studied CYPs and transporters at therapeutic concentrations.

Question on clinically relevant specifications (TBD)?

None.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7. All Clinical Studies

Trial ID	Phase	Country/ Region	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
CXA-ICU-14-01 7625A-007	1	USA (including Puerto Rico) EU (Belgium, France, Germany, Italy, Spain)	A Phase 1, Prospective, Multicenter, Open-label Study to Assess the Plasma Pharmacokinetics and Lung Penetration of Intravenous (IV) ceftolozane/tazobactam in Critically Ill Patients	Non-comparative, open-label, prospective, multicenter to assess plasma PK and intrapulmonary penetration (epithelial lining fluid [ELF] concentrations)	Group 1: CrCL >50 mL/min: ceftolozane/tazobactam (C/T) 3 g IV q8h, 4-6 doses CrCL 30-50 mL/min: C/T 1.5 g IV q8h, 4-6 doses CrCL 15-29 mL/min: C/T 750 mg IV q8h, 6 doses Group 2: C/T 3 g IV single dose	Males/females Group 1: Ages 21-88 years; 26 ventilated patients with pneumonia receiving concurrent antibacterial therapy Group 2: Ages: 20-50 years; 10 critically ill patients with CrCL ≥180 mL/min	Group 1: C/T 3 g IV q8h (21 patients); C/T 1.5 g IV q8h (4 patients); C/T 0.75 g IV q8h (1 patient); Group 2: C/T 3 g IV single dose (10 patients)

Trial ID	Phase	Country/ Region	Trial Title	Trial Design	Dosing Regimen	Trial Population	Subject Exposure
CXA-EB-13-05 7625A-018	1	USA	A Single-dose, Open-label, Parallel-group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ceftolozane/Tazobactam Administered Intravenously to Adult Japanese, Chinese and Caucasian Healthy Subjects	Open-label, parallel group	Ceftolozane/ tazobactam 1.5 g IV single dose on Day 1; and Ceftolozane/ tazobactam 3 g IV single dose on Day 4	Male/female Age: 20-50 Caucasian, Chinese, and Japanese healthy subjects	Ceftolozane/ tazobactam 1.5 g IV (Day 1): 29 subjects (Caucasian: 10; Chinese: 9; and Japanese: 10) Ceftolozane/ tazobactam 3 g IV (Day 4): 27 subjects (Caucasian: 10; Chinese: 8; and Japanese: 9)
CXA-NP-11-04 7625A-008	3	Global	A Prospective, Randomized, Double-Blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia	Randomized, double-blind, prospective, multicenter	Ceftolozane/ tazobactam 3000 mg q8h IV or Meropenem 1000 mg q8h IV administered for a minimum of 8 days up to maximum 14 days	Male/female Age: ≥18 years Subjects with VABP and ventilated HABP stratified by diagnosis and by age (≥65 or <65 years) Planned enrollment: 726 subjects	Ceftolozane/ tazobactam 3000 mg: 361 patients Meropenem 1000 mg: 359 patients

7.2. Review Strategy

This review focuses on Study PN008 (CXA-NP-11-04), "A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia", to support the safety and efficacy of ceftolozane/tazobactam for the treatment of HABP/VABP. The results from 3 Phase 1 studies (PN018, PN028 and PN007) were also reviewed as they provided additional support for the administration of ceftolozane/tazobactam at a dose of 3 g every 8 hours for the HABP/VABP indication. These studies will be discussed in Section 6, by Dr. Anthony Nicasio, the primary Clinical Pharmacology reviewer. Due to differences in study design and the small sample size, the Phase 1 studies will not be pooled for the review of safety, performed by Dr. Maria Allende, M.D., the primary Clinical reviewer. Efficacy results were reviewed by Dr. Cheryl Dixon, Ph.D., the primary Statistical reviewer. As this is a marketed product, and the Applicant is not proposing a different formulation for the HABP/VABP indication, some sections of the review template do not apply to this review. They are noted or deleted where appropriate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design - Study PN008

Trial Design

PN008 was a Phase 3, randomized, double-blind, multicenter, active-controlled noninferiority study designed to assess the safety and efficacy of ceftolozane/tazobactam compared with meropenem in the treatment of adult subjects with vHABP or VABP due to Gram-negative pathogens. (For the purposes of this review, HABP and vHABP will be used interchangeably.) A total of 726 patients aged 18 years and older, of whom at least 50% had a diagnosis of VABP, were randomized 1:1 to receive ceftolozane/tazobactam 3g Q8 (N=362) or meropenem 1g Q8 (N=364) for a total of 8 to 14 days. Both ceftolozane/tazobactam and meropenem were administered intravenously over 60 minutes. Ceftolozane/tazobactam and meropenem doses were adjusted for moderate and severe renal insufficiency (Table 8 and Table 9).

Table 8. Ceftolozane/Tazobactam Dose Adjustment for Renal Insufficiency in Study PN008 (Infusions Over 60 Minutes)

Renal Status (CrCL Range)	Ceftolozane/Tazobactam (TOL/TAZ) Dose
CrCL>50 mL/min	3 g (2 g TOL/ 1g TAZ) q8h
Moderate impairment (30 mL/min≤CrCL≤50 mL/min)	1.5 g (1 g TOL/0.5 g TAZ) q8h
Severe impairment (15 mL/min≤CrCL≤29 mL/min)	750 mg (500 mg TOL/250 mg TAZ) q8h
ESRD	2.25 g (1.5 g TOL/0.75 g TAZ) loading dose followed by 450 mg (300 mg TOL/150 mg TAZ) q8h for the remainder of the treatment period. On hemodialysis days, the dose should be administered at the earliest possible time following completion of dialysis

Abbreviations: CrCL=creatinine clearance; ESRD=end stage renal disease; g=gram; mg=milligram; min=minute; mL=milliliter; q8h=every 8 hours; TAZ=tazobactam; TOL=ceftolozane.

Table 9. Meropenem Dose Adjustments for Renal Insufficiency in Study PN008 (Infusions Over 60 Minutes)

Renal Function	Dose	Infusion Frequency
CrCL>50 mL/min	1000 mg IV	q8(±2)h
CrCL 30 - 50 mL/min	1000 mg IV	q12(±2)h
CrCL 26 - 29 mL/min	1000 mg IV	q12(±2)h
CrCL 15 - 25 mL/min	500 mg IV	q12(±2)h
CrCL<15 mL/min	Discontinue study drug	

Subjects were required to receive adjunctive Gram-negative therapy with aminoglycosides for up to 72 hours pending culture results at sites with >15% prevalence of carbapenem-resistant *P. aeruginosa*.

Randomization was stratified by diagnosis (vHABP or VABP) and by age (<65 and >65 years). Randomization was also blocked by region using the following regions: North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific, and Rest of the World. Forced randomization was enabled within the randomization system for this study to prevent potential unblinding of site personnel. Due to limited study drug storage at the sites, it was possible for a site to run out of one of the study drugs but still have the other study drug available. In the event that drug supply availability issues arose at a site during the study, the randomization system "forced" a subject to be allocated to the next free number in the randomization list that corresponded to the treatment available at the site. This was allowed only for a limited number of randomizations and the randomization system tracked subjects who eventually backfilled the originally intended randomization slot. While this was intended to prevent unblinding at the study site and the Applicant states that forced randomization did not lead to any premature unblinding, one cannot guarantee that the investigators did not know the availability of study drug at their site. Any impact of this will be assessed in a sensitivity analysis.

Subject evaluations were performed over three phases: Screening (Days -1 to 1), Treatment (Days 1 to 14) and Post-Treatment: EOT (within 24 hrs of last dose), Day 14, TOC (7 to 14 days after EOT), Day 28 and LFU (28 to 35 days after EOT) visits.

Table 10. Study Design

Screening	Treatment	EOT	D 14[a]	TOC	D 28[a]	LFU
Day -1 to 1	Days 1 to 14	Within 24 hours after last dose of study drug	Day 14	7 to 14 days after the EOT	Day 28	28 to 35 days after the EOT
Assess eligibility, collect LRT specimen, randomize to treatment	Infuse blinded IV study therapy (ceftolozane/tazobactam 3000 mg q8h or meropenem 1000 mg q8h), Total duration of study drug administration is a minimum of 8 days (24 doses) and up to a maximum of 14 days (42 doses)[b]	Evaluation for assessment of microbiological response, clinical response, and safety	Assess for all-cause mortality	Subjects return to study center for primary assessment of microbiological response, clinical response, and safety	Assess for all-cause mortality	Evaluation for final assessment of clinical response and safety

Abbreviations: D = day; EOT = end-of-therapy visit; IV=intravenous; LFU = late follow-up visit; LRT= lower respiratory tract; mg = milligram; q8h=every 8 hours; TOC = test-of-cure visit.
[a] If TOC visit and LFU visit are not on Day 14 and Day 28, respectively, an assessment of all-cause mortality must be conducted independently.
[b] The total number of infusions may increase if a dose adjustment is required based on renal function due to the addition of placebo infusions to maintain the blind.
Source: Table 9-1 from CSR

Eligibility Criteria

Subjects had to meet the following inclusion criteria to be eligible for the trial:

- Males or females (not pregnant or nursing) aged 18 years or older and agreeing to appropriate contraception
- Intubated (via endotracheal tube, including tracheostomy patients) and on mechanical ventilation at the time of randomization:
- **For Ventilated HABP (vHABP):**
  - At least 1 of the following signs and/or symptoms must be present within the 24 hours **prior** to intubation OR within the 48 hours **after** intubation in a patient who has been either hospitalized for ≥48 hours or who has been discharged from a hospital within the prior 7 days (includes patients institutionalized in skilled nursing or other long-term care facility):
    - A new onset of cough (or worsening of baseline cough)
    - Dyspnea, tachypnea, or respiratory rate greater than 30 per minute, particularly if any or all of these signs or symptoms are progressive in nature
    - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air, OR worsening of the ratio of PaO_2/FiO_2
- **For VABP:**
  - Receiving mechanical ventilation ≥48 hours and at least 1 of the following:
    - Acute changes made in the ventilator support system to enhance oxygenation, as determined by worsening partial pressure of oxygen on arterial blood gas, or worsening PaO_2/FiO_2
    - Hypoxemia defined as an arterial blood gas partial pressure of oxygen less than 60 mmHg while the subject is breathing room air, OR a pulse oximetry oxygen saturation less than 90% while the subject is breathing room air, OR worsening of the ratio of PaO_2/FiO_2
- Chest radiograph (or CT scan) obtained within the 24 hours prior to the first dose of study drug shows the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.
- Have the following clinical criteria within the 24 hours prior to the first dose of study drug:
  - Purulent tracheal secretions
  - And at least 1 of the following:
    - Documented fever (body temperature ≥38°C [104◦F])
    - Hypothermia (body temperature ≤35°C [95.2◦F])
    - WBC count ≥10,000 cells/mm^3
    - WBC count ≤4,500 cells/mm^3
    - ≥15% immature neutrophils
- Have a baseline lower respiratory tract specimen obtained for Gram stain and quantitative culture within 36 hours prior to the first dose of study drug. This specimen can be obtained by a BAL, mini-BAL, PBS, or an ETA;

A subject was not eligible if they met any of the following exclusion criteria:

- Any of the following diagnoses or conditions that interfere with the assessment or interpretation of outcome:
    - Atypical, viral or fungal (including *Pneumocystis jiroveci*), known or suspected community acquired pneumonia
    - Tracheobronchitis (without documented pneumonia), chemical pneumonitis, or post-obstructive pneumonia
    - Active primary or metastatic lung cancer
    - Pleural effusions (or empyema) requiring therapeutic drainage, lung abscess, or bronchiectasis
    - Cystic fibrosis, acute exacerbation of chronic bronchitis, or active pulmonary tuberculosis
    - NYHA Stage IV Congestive Heart Failure or Cirrhotic Liver Disease
    - Full thickness burns (greater than 15% of total body surface area)
    - Severe confounding respiratory condition due to penetrating chest trauma (i.e., chest trauma with paradoxical respiration)
- Received systemic or inhaled antimicrobial therapy effective against gram-negative pathogens that cause HABP/VABP for > 24 hours in the 72 hours prior to the first dose of study drug.
  Exceptions:
    - Persistent/worsening signs and/or symptoms of HABP/VABP are still present despite >48 hours of antibacterial therapy for the treatment of the current HABP/VABP, and (a) an LRT culture obtained while the subject is on the failing antibacterial therapy for this episode of HABP/VABP showed growth of a gram-negative pathogen and (b) the isolated pathogen is not known to be resistant to one of the study drugs.
    - Signs and/or symptoms of HABP/VABP develop after receiving ≥48 hours of antibacterial therapy for treatment of an infection other than the current HABP/VABP. NOTE: Subjects on ≥48 hours of antibacterial therapy for infection prophylaxis (rather than treatment for a documented or suspected infection) are not eligible for enrollment under this exception.
    - Treatment with a non-adsorbed antibiotic used for gut decontamination (e.g., low-dose erythromycin) or to eradicate *C. difficile*.
- Baseline Gram stain shows the presence of only Gram-positive bacteria. **Exception**: if the subject has a lower respiratory tract culture growing a gram-negative pathogen obtained within 72 hours prior to the first dose of study drug, these results will supersede baseline Gram stain results of only gram-positive bacteria.
- Active immunosuppression
- Receipt of >24 hours of carbapenem within 7 days prior to the first dose of study drug;
- Growth of a meropenem-resistant or ceftolozane/tazobactam-resistant, Gram-negative pathogen from a respiratory or blood culture, within 15 days prior to the first dose of study drug;

- Development of end-stage renal disease defined as creatinine clearance <15mL/min, OR requirement of peritoneal or hemodialysis or hemofiltration, OR a urine output <20mL/hour over a 24-hour period;
- The presence of any of the following:
  - ALT or AST >3 x ULN
  - Total bilirubin >2 x ULN
  - Alkaline Phosphatase >4 x ULN
  - Hematocrit <21% or hemoglobin <7 g/dL
  - Neutropenia with absolute count <500/mm^3
  - Platelet count <50,000/mm^3
- Expected survival <72 hours
- Any condition or circumstance that, in the opinion of the investigator, would compromise the safety or the quality of the study data.
- Anticipated concomitant use of any of the following medications during the course of study therapy (through EOT visit): valproic acid or divalproex sodium. For subjects who will receive linezolid as gram-positive adjunctive therapy, anticipated concomitant use of serotonin re-uptake inhibitors, tricyclic antidepressants, or serotonin 5-HT1 receptor agonists (triptans), meperidine, or buspirone during the course of linezolid treatment.
- For subjects who will receive linezolid as gram-positive adjunctive therapy, receipt of a monoamine oxidase inhibitor within 14 days prior to the first dose of study drug or anticipated concomitant use during linezolid therapy.

Study Endpoints

The primary efficacy endpoint was Day 28 all-cause mortality in the ITT population. This follows the draft Guidance for Industry on developing drugs for the treatment of HABP/VABP which recommends the primary endpoint for a confirmatory trial be based on all-cause mortality evaluated at a fixed timepoint at any time between day 14 and day 28.

The key secondary efficacy endpoint was clinical response at the TOC visit in the ITT population. Clinical response was based on the assessment of clinical signs and symptoms of HABP/VABP, whether additional antibacterial therapy was administered for HABP/VABP except for approved adjunctive therapy, and survival status. A favorable clinical response was a clinical cure (see Table 11).

Additional secondary efficacy endpoints included clinical response at EOT and the LFU visit and microbiological outcome assessments made at the EOT and TOC visits. Microbiological assessments were determined by the Applicant based on the results of the lower respiratory tract culture at the appropriate visit. Microbiological response was classified per-pathogen as well as per-subject.

The definitions for clinical and microbiological responses are presented in the following tables.

Table 11. Clinical Response Categories at the EOT and TOC Visit

Outcome	Definition
Cure	Complete resolution of all or most of the clinical signs and symptoms of VABP/vHABP which were present at baseline, AND No new signs, symptoms or complications attributed to VABP/vHABP, AND No additional antibiotic therapy administered for VABP/vHABP, except for the approved adjunctive therapy, AND Patient is alive
Failure	Progression, relapse, or recurrence of new symptoms or complications attributable to VABP/vHABP, OR Lack of resolutions (persistence), insufficient improvement in signs and symptoms of VABP/vHABP which were present at baseline, study drug discontinuation due to resistant LRT pathogens, or need for alternative or prolonged antibiotic therapy for treatment of VABP/vHABP, OR Patient died of VABP/vHABP
Indeterminate	Subject prematurely discontinued study drug due to No Growth or only *S. aureus* isolated from the baseline LRT culture, OR Study data not available for the evaluation of efficacy for any reason including: Lost to follow-up Withdrawal of consent Subject died from cause other than VABP/vHABP Randomized not treated

Source: Table 3 of Statistical Analysis Plan for Protocol PN008

Table 12. Microbiologic Outcome Categories at the EOT and TOC Visits

	Definition
Per-Pathogen Outcome	
Eradication	Absence defined as ≥1-log reduction in bacterial burden of the original baseline LRT pathogen AND a per pathogen count of $\leq 10^4$ CFU/mL for an ETA or sputum specimen, $\leq 10^3$ CFU/mL for a BAL specimen, or $\leq 10^2$ CFU/mL for a PBS specimen from a follow-up LRT culture
Presumed eradication	Absence of material to culture (e.g., inability to obtain a culture in an extubated subject) in a subject deemed a clinical cure
Persistence	Continued presence of the original causative baseline pathogen(s) from an LRT culture obtained at or after EOT
Presumed persistence	Absence of material to culture in a subject deemed a clinical failure
Indeterminate	Absence of respiratory material to culture at the EOT and TOC in a subject with Indeterminate clinical response
Recurrence (at the TOC visit)	Isolation of the original causative bacterial baseline pathogen(s) at the appropriate diagnostic threshold from an LRT culture in a subject with documented eradication at the EOT visit
Per Subject Outcome	
Microbiologic cure or presumed cure	All baseline pathogens are deemed eradicated/presumed eradication or absence of respiratory material to culture at the EOT or TOC in a subject deemed a clinical cure
Microbiologic failure or presumed failure	Any baseline pathogen is deemed persistent/presumed persistent or absence of material to culture in a subject deemed a clinical failure
Indeterminate	Absence of respiratory material to culture at the EOT or TOC in a subject with Indeterminate clinical response

Source: Tables 4 and 5 of Statistical Analysis Plan for Protocol PN008

Statistical Analysis Plan

The study had separate primary and key secondary objectives defined for the US FDA and European Medicines Agency (EMA). This section is based on the statistical analysis plan for the US FDA.

Analysis Populations

The ITT population consisted of all randomized subjects, regardless of whether or not they received study drug. The primary efficacy analysis population was the ITT population. Subjects in the ITT population were analyzed based on the treatment arm to which they were randomized.

The Safety population includes all randomized subjects who received any amount of study drug. All safety analyses were performed on this population. Subjects in the Safety population were analyzed based on the actual treatment they received.

The microbiological ITT (mITT) population was a subset of the ITT population who received any amount of study drug and had at least 1 bacterial respiratory pathogen isolated from the baseline lower respiratory tract (LRT) culture that was susceptible to at least 1 of the study drugs. Subjects with *S. aureus* as their only baseline LRT pathogen were excluded from the mITT population. Possible concerns regarding the definition of the mITT population will be discussed in Section 8.1.2 under Efficacy Results – Secondary and other relevant endpoints.

Two evaluable populations were defined in the protocol: the Clinically Evaluable (CE) and the Microbiologically Evaluation (ME) populations. These populations were subsets of the ITT and mITT populations, respectively, including subjects who adhered to the study protocol through the TOC visit and had an evaluable clinical outcome at the TOC visit. Additionally, to be eligible for the ME population, sufficient bacterial pathogen loads had to be detected. These populations were used for supportive efficacy analyses. Since eligibility in the evaluable populations is based in part on post-randomization criteria which may be related to the study drug, the focus of efficacy analyses presented in this review will be the ITT and mITT populations.

A subject's eligibility for a given analysis population was determined by the Technical Assessment Group (TAG) in accordance with the Population and Outcome Process Plan (POPP). The POPP described the processes through which population assignment and outcome response were manually reviewed, determined, and documented for the study. All assessments were made while the study was still blinded.

Analysis Methods

The primary analysis of Day 28 all-cause mortality is based on the 2-sided 95% confidence interval for the treatment difference (meropenem - ceftolozane/tazobactam) stratified by diagnosis (VABP or vHABP) and age (< 65 or ≥65 years). The difference in proportions will be calculated as a weighted average across all strata constructed using Mehrotra-Railkar continuity-corrected minimum-risk (MRc) stratum rates. The 2-sided 95% confidence interval for the treatment difference will be calculated as a stratified Newcombe confidence interval constructed using the MRc weights. The stratification factors are based on the actual stratum. A subject whose mortality outcome is missing or unknown will be analyzed as deceased. Ceftolozane/tazobactam will be considered non-inferior to meropenem if the lower limit of the 2-sided 95% confidence intervals for the treatment difference (meropenem - ceftolozane/tazobactam) is greater than -10%.

The analysis of clinical response at the TOC visit will be conducted using similar methods. However, the treatment difference will be calculated as ceftolozane/tazobactam – meropenem. A subject with a missing clinical response will be categorized as a treatment failure. Ceftolozane/tazobactam will be considered non-inferior to meropenem if the lower limit of the 2-sided 95% confidence intervals for the treatment difference (ceftolozane/tazobactam - meropenem) is greater than -12.5%.

To maintain an overall 1-sided 0.025 type I error rate across the primary and key secondary efficacy endpoints, a sequential testing approach will be used. First, non-inferiority of Day 28 all-cause mortality in the ITT population will be evaluated. If non-inferiority is demonstrated, then non-inferiority of favorable clinical response at the TOC visit in the ITT population will be evaluated.

Sensitivity analyses of the primary efficacy endpoint and key secondary endpoint include calculation of 95% confidence intervals about the treatment difference unadjusted for the stratification factors, an analysis performed using the stratum designated at randomization, and an analysis excluding forced randomized subjects.

For analyses of other dichotomous endpoints including per-pathogen microbiological response and subgroup analyses, the 2-sided 95% confidence intervals for the treatment difference will be calculated as unstratified Newcombe confidence intervals. Planned subgroup analyses include the following subgroups: region (North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific, Rest of the World); diagnosis at baseline (VABP, vHABP); age (<65, ≥65 years); sex (male, female); baseline creatinine clearance (<15, 15 to <30, 30 to 50, >50 to <80, ≥80); failure of prior antibiotic therapy for HABP/VABP (yes, no); prior antibiotic use (yes, no); baseline APACHE score (< 20, ≥20); bacteremic at baseline (yes, no); baseline Gram-negative adjunctive therapy (yes, no); baseline Gram-positive adjunctive therapy (yes, no); baseline LRT pathogen (*P. aeruginosa*, Enterobacteriaceae); and number of baseline LRT pathogens (monomicrobial, polymicrobial).

***Reviewer's Comment**: The trial design is generally consistent with the HABP/VABP guidance. Although meropenem is not approved in the United States specifically for the treatment of HABP/VABP, it was considered an appropriate comparator for the study as it has been used as the comparator in other recent HABP/VABP studies. The non-inferiority margin of 10% for the primary endpoint of Day 28 all-cause mortality has been justified in the HABP/VABP guidance. A data driven justification of the 12.5% non-inferiority margin for clinical response has not been established. Therefore, this margin is used for descriptive purposes only.*

Sample Size Calculation

Assuming a Day 28 all-cause mortality rate of 20% in both treatment arms, a non-inferiority margin of 10%, and a 1-sided significance level of 0.025, a sample size of 726 subjects (363 per arm) in the ITT population will have 90% power to demonstrate non-inferiority of ceftolozane/tazobactam to meropenem with respect to the difference in Day 28 all-cause mortality.

Interim Analysis

A review of the data was performed by an independent Data Safety Monitoring Board (DSMB) when approximately 30% of patients were enrolled and completed the study. At the interim analysis, consideration to stopping the study early for futility only was allowed based on the 28-day all-cause mortality rate. Since only stopping for futility was allowed, no adjustment to the type I error rate was made at the final analysis. Following the interim analysis at approximately 30%, the DSMB recommended that the study continue as is but requested an additional DSMB meeting for an additional safety assessment once approximately 2/3 of the study subjects were enrolled. At this meeting, all-cause mortality through all follow-up was provided to assess if there was a mortality safety issue. However, no formal efficacy analysis on 28-day all-cause mortality was provided. No changes to the study were recommended following the second interim analysis.

Protocol Amendments

The original protocol was dated May 11, 2012. There were 10 protocol amendments (6 global amendments and 4 country-specific amendments, resulting in 7 versions of the protocol). Versions 1 through 4 occurred prior to any subject enrollment. Nine subjects were then enrolled under Protocol Version 4. The rationale and key changes that occurred in Versions 5 to 7 and the number of subjects enrolled in each version are summarized below:

1. Amendment Number: MK-7625A-008-04 (Protocol Version 5.0)
   Date: 22-OCT-2014. Number of Subjects Enrolled in Protocol Version: 199

   Rationale and Key Changes:
   - The minimum proportion of subjects with VABP as the baseline diagnosis was increased to 50% (from 30%) to align with the updated FDA draft guidance on drug development for treatment of HABP/VABP.

- Additional detail was added to Exclusion Criterion #3 (prior antibiotics) to further clarify the allowance for prior antibiotics administered for an indication other than HABP/VABP.
- Alternative Gram-positive adjunctive therapy was permitted in subjects who had a contraindication to receiving linezolid. Alternative Gram-negative adjunctive therapy was permitted in subjects who had a contraindication to receiving amikacin.
- Clarification was provided for making study drug treatment decisions, including adjunctive therapy, following the results of the baseline LRT culture. Based on the results of the baseline respiratory culture, the investigator had discretion for continuing or discontinuing study drug and the applicable adjunctive therapy based on the subject's clinical presentation.
- Clarified that clinical failures, including the following, were NOT AEs: progression, relapse, or recurrence of new symptoms or complications attributable to HABP/VABP, as well as lack of resolution (persistence) or insufficient improvement in signs and symptoms of HABP/VABP which were present at baseline that required new or prolonged antibiotic therapy. As such, these were not be captured as AEs in the study.
- The DSMB charter was amended to include only an evaluation for futility during the interim analysis. Therefore, it was no longer necessary to adjust the type I error rate in this study.

2. Amendment Number: MK-7625A-008-05 (Protocol Version 6.0)
   Date: 15-MAR-2016. Number of Subjects Enrolled in Protocol Version: 433

   Rationale and Key Changes:
   - Removed APACHE II score as an inclusion criterion since it was no longer required as an entry criterion in regulatory guidance documents.
   - Changed treatment duration of study drug from a fixed duration of 8 days (with extension to 14 days only when Pseudomonas was isolated from baseline culture) to a treatment duration range of 8 to 14 days regardless of the organism isolated at baseline. This allowed for longer treatment duration in subjects that are responding to treatment at 8 days but are felt by the Investigator to require additional treatment.
   - If a prior LRT culture taken within 72 hours prior to the first dose of study drug produced a Gram-negative pathogen, this confirmed a case of Gram-negative bacterial pneumonia and took precedence over the results of a baseline Gram stain that showed only gram-positive bacteria.
   - Exclusion Criterion #6 was modified to allow for the entry of subjects who had ≤24 hours of a carbapenem within the 7 days prior to the first dose of study drug. Previously, any carbapenem use within the prior 15 days was excluded. This modification conservatively broadens the eligibility criteria while still limiting the risk of selecting for carbapenem resistant pathogens by restricting the amount of prior carbapenem exposure.

3. Amendment Number: MK-7625A-008-08 (Protocol Version 7.0)
   Date: 25-AUG-2017. Number of Subjects Enrolled in Protocol Version: 85

   Rationale and Key Changes:
   - Sole key secondary endpoints were established for both EMA and FDA (Day 28 all-cause mortality and clinical response at TOC in the ITT population, respectively) to prioritize secondary analyses. The SAP was updated to align with these changes.

8.1.2. Study Results – Study PN008

Compliance with Good Clinical Practices

The Applicant has attested that, "… the study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding Independent Ethics Committee review, informed consent, and the protection of human subjects in biomedical research..."

Financial Disclosure

Please refer to Section 15.2, where this is discussed in detail.

Data Quality and Integrity

The statistical and clinical review teams evaluated the data and analysis quality with assistance from the Office of Computational Science (OCS). This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the availability of appropriate variables, variables populated by expected data points and the appropriate use of standard terminology. In general, the data submitted by the Applicant was acceptable and there are no issues noted with regard to the data quality and integrity. Inspections done by the Office of Scientific Investigations did not reveal any significant irregularities in the conduct of the trial at the selected study sites.

Patient Disposition

A total of 726 subjects were randomized in the study: 362 subjects to ceftolozane/tazobactam and 364 subjects to meropenem. Six of the randomized subjects did not receive any study drug: 1 subject in the ceftolozane/tazobactam group (due to withdrawal of consent prior to dosing) and 5 subjects in the meropenem group (4 due to not meeting inclusion/exclusion criteria and 1 due to no longer needing treatment for VABP/vHABP per investigator discretion). The percentage of subjects completing treatment with study drug and completing the study were generally similar between the two treatment groups. Overall 73% of randomized subjects completed treatment with study drug. The most common reasons for discontinuing treatment early were due to an adverse event or insufficient therapeutic response. Approximately 68% of

randomized subjects completed the study through the last study visit per the protocol. The most common reason for premature withdrawal from the study was due to adverse events, of which, the majority resulted in death.

Table 13. Patient Disposition

Patient Category	Ceftolozane/Tazobactam	Meropenem
Randomized	362	364
Did not receive study drug	1 (0.3)	5 (1.4)
Completed study drug	263 (72.6)	271 (74.5)
Discontinued study drug prematurely	98 (27.1)	88 (24.2)
Adverse event	36 (9.9)	42 (11.5)
Insufficient therapeutic effect	23 (6.4)	15 (4.1)
All baseline LRT pathogens resistant to both study drugs	13 (3.6)	11 (3.0)
Physician decision	8 (2.2)	7 (1.9)
Gram-negative adjunctive therapy continued > 72 h or study treatment regimen changed	4 (1.1)	2 (0.5)
No growth or only *S. aureus* isolated at baseline	4 (1.1)	4 (1.1)
Development of end stage renal disease	3 (0.9)	0
Protocol deviation	2 (0.6)	1 (0.3)
Withdrawal by subject	2 (0.6)	1 (0.3)
Other	2 (0.6)	5 (1.4)
Lost to follow-up	1 (0.3)	0
Completed study	245 (67.7)	250 (68.7)
Discontinued study prematurely	117 (32.3)	114 (31.3)
Adverse event	107 (29.6)	99 (27.2)
Lost to follow-up	7 (1.9)	4 (1.1)
Other	2 (0.6)	2 (0.5)
Withdrawal by subject	1 (0.3)	3 (0.8)
Protocol deviation	0	4 (1.1)
Physician decision	0	2 (0.5)

Source: Reviewer's analysis based on ADSL analysis dataset

The ITT population included all randomized subjects: 362 subjects on ceftolozane/tazobactam and 364 subjects on meropenem. The Safety population was a subset of the ITT population excluding the six randomized subjects who did not receive any study drug. All subjects received their randomly assigned treatment.

The mITT population consisted of 264 ceftolozane/tazobactam subjects and 247 meropenem subjects. Subjects were excluded from the mITT population primarily because no pathogen was identified at baseline (30 ceftolozane/tazobactam and 44 meropenem subjects) or all baseline pathogens identified were non-susceptible to both study drugs (53 ceftolozane/tazobactam and 48 meropenem subjects). Thirteen subjects in each treatment arm were excluded from the mITT population because a non-streptococcal species Gram-positive organism was the only baseline pathogen identified. Of the subjects included in the mITT population, 237 (89.8%) ceftolozane/tazobactam subjects and 219 (88.7%) meropenem subjects had all baseline pathogens susceptible to meropenem and 190 (72.0%) ceftolozane/tazobactam subjects and 185 (74.9%) meropenem subjects had all baseline pathogens susceptible to both study drugs.

The CE population consisted of 218 ceftolozane/tazobactam subjects and 221 meropenem subjects. The most common reasons for exclusion from the CE population included no evaluable clinical response at TOC (17.4% for ceftolozane/tazobactam and 20.1% for meropenem) and for receipt of effective concomitant therapy before the TOC visit and the subjects was not a failure (13.3% for ceftolozane/tazobactam and 14.0% for meropenem).

The ME population consisted of 115 ceftolozane/tazobactam subjects and 118 meropenem subjects. Subjects were primarily excluded from the ME population because they were excluded from the mITT and/or CE populations (190 ceftolozane/tazobactam and 195 meropenem subjects). The majority of the remaining subject exclusions from the ME population were due to having an insufficient bacterial load (49 ceftolozane/tazobactam and 41 meropenem subjects).

Table 14. Analysis Populations

Population	Ceftolozane/Tazobactam	Meropenem
Randomized (ITT)	362 (100)	364 (100)
Safety	361 (99.7)	359 (98.6)
mITT	264 (72.9)	247 (67.9)
Clinically evaluable	218 (60.2)	221 (60.7)
Microbiologically evaluable	115 (31.8)	118 (32.4)

Protocol Violations/Deviations

Overall, 105 (29.0%) ceftolozane/tazobactam subjects and 124 (34.1%) meropenem subjects were considered by the Applicant to have at least 1 important protocol deviation during the trial. The types of protocol deviations and incidences were similar between the treatment groups. The most frequently reported deviations were related to study intervention [47 (13.0%) ceftolozane/tazobactam subjects and 48 (13.2%) meropenem subjects] and trial procedures [41 (11.3%) ceftolozane/tazobactam subjects and 54 (14.8%) meropenem subjects] categories.

Within the study intervention category, the majority of the individually reported protocol deviations occurred at rates of 2% or less and were not expected to compromise the interpretability of the trial results. The exception is the deviation of participants with renal impairment who received a study treatment dosing schedule not consistent with that specified for their renal function which occurred in 19 (5.2%) ceftolozane/tazobactam subjects and 17 (4.7%) meropenem subjects. Since ceftolozane/tazobactam and meropenem require dosing adjustment for those with impaired renal function, it is possible that not receiving the appropriate dose may have an impact on response; however, the rates of protocol deviations of this kind were similar. Subgroup analyses for the primary and key secondary endpoints by baseline renal function were conducted which may assess any impact this may have had.

The primary protocol deviation in the trial procedures category was participant mis-stratified at the time of randomization. This occurred in 26 (7.2%) ceftolozane/tazobactam subjects and 32

(8.8%) meropenem subjects. All but one of the mis-stratifications was with regard to the primary diagnosis. The other was with regard to age at randomization. Use of an incorrect randomization stratification factor would not be expected to impact the integrity of the analysis. This essentially reduces to stratifying the randomization on a different variable than intended but still allows for an unbiased estimate of a treatment effect. However, sensitivity analyses for the primary and key secondary endpoints were conducted based on the stratification category at randomization.

Demographic and Baseline Characteristics

The following table summarizes the demographic and baseline characteristics in the ITT population. The treatment groups were generally comparable with respect to most of the demographic and baseline characteristics.

The majority of the subjects were male and white. The mean age was 60 years of age and approximately 44% were 65 years or older. The study was primarily conducted in Eastern Europe. Less than 5% of the subjects were from sites in the United States (North America).

The population consisted of seriously ill subjects. All subjects were ventilated at baseline and VABP accounted for 71.5% of the HABP/VABP diagnoses. The median APACHE II score was 17. A higher percentage of ceftolozane/tazobactam subjects (17.7%) subjects than meropenem subjects (11.3%) were bacteremic with any pathogen at baseline. Approximately 88% of the subjects had prior antibacterial use before randomization and approximately 79% of the subjects received prior Gram-negative antibacterial therapy before randomization. Approximately 12% of the subjects had failed prior antibacterial therapy for HABP/VABP. Approximately 36% of the subjects (37.1% for TOL/TAZ and 34.3% for meropenem) had some level of renal impairment at baseline. Three-quarters of the subjects had been hospitalized at least 5 days before randomization and about half were on mechanical ventilation for at least 5 days before randomization.

The majority of subjects received adjunctive Gram-positive therapy at baseline as required by the protocol. Additionally, approximately 30% of subjects received adjunctive Gram-negative therapy at baseline as allowed by the protocol until baseline culture results were available.

Table 15. Demographic and Baseline Characteristics (ITT Population)

Characteristic	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)
Sex		
Male	262 (72.4)	255 (70.1)
Female	100 (27.6)	109 (29.9)
Age (years)		
Mean (SD)	60.5 (16.7)	59.5 (17.2)
Median	62.5	62
Min, Max	18, 98	18, 92
Age Group		
18 to 44 years	64 (17.7)	76 (20.9)
45 to 64 years	138 (38.1)	128 (35.2)
65 to 74 years	77 (21.3)	84 (23.1)
≥75 years	83 (22.9)	76 (20.9)
Race		
White	301 (83.1)	300 (82.4)
Black or African American	10 (2.8)	4 (1.1)
Asian	27 (7.5)	23 (6.3)
American Indian or Alaska Native	0	1 (0.3)
Native Hawaiian or other Pacific Islander	1 (0.3)	0
Other	4 (1.1)	7 (1.9)
Not Reported	19 (5.2)	27 (7.4)
Missing	0	2 (0.5)
Ethnicity		
Hispanic or Latino	25 (6.9)	24 (6.6)
Not Hispanic or Latino	305 (84.3)	278 (76.4)
Not Reported	29 (8.0)	56 (15.4)
Unknown	3 (0.8)	4 (1.1)
Missing	0	2 (0.5)
Primary Diagnosis		
VABP	263 (72.7)	256 (70.3)
Ventilated HABP	99 (27.3)	108 (29.7)
APACHE II Score		
N	361	362
Mean (SD)	17.5 (5.2)	17.4 (5.7)
Median	17	17
Min, Max	2, 33	2, 39
Creatinine Clearance (mL/min)		
≥150 (hyperclearance)	67 (18.5)	64 (17.6)
≥80 to <150 (normal)	160 (44.2)	172 (47.3)
>50 to <80 (mild impairment)	82 (22.7)	77 (21.2)
≥30 to ≤50 (moderate impairment)	35 (9.7)	26 (7.1)
≥15 to <30 (severe impairment)	17 (4.7)	21 (5.8)
<15 (ESRD)	0	1 (0.3)
Missing	1 (0.3)	3 (0.8)

Characteristic	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)
Failed Prior Antibacterial Therapy for HABP/VABP		
Yes	53 (14.6)	40 (11.0)
No	309 (85.4)	323 (88.7)
Missing	0	1 (0.3)
Prior Antibiotic Use		
Yes	318 (87.8)	323 (88.7)
No	44 (12.2)	41 (11.3)
Prior Gram-Negative Antibacterial Therapy		
Yes	285 (78.7)	288 (79.1)
≤24 hours	95 (26.2)	95 (26.1)
>24 hours	190 (52.5)	193 (53.0)
No	77 (21.3)	76 (20.8)
Bacteremic		
Yes	64 (17.7)	41 (11.3)
No	298 (82.3)	323 (88.7)
Baseline Gram-Negative Adjunctive Therapy		
Yes	103 (28.5)	112 (30.8)
No	258 (71.3)	246 (67.6)
Missing	1 (0.3)	6 (1.6)
Baseline Gram-Positive Adjunctive Therapy		
Yes	350 (96.7)	349 (95.9)
No	11 (3.0)	12 (3.3)
Missing	1 (0.3)	3 (0.8)
Duration of Mechanical Ventilation Prior to Randomization		
<5 days	178 (49.2)	184 (50.5)
≥5 days	182 (50.3)	176 (48.4)
missing	2 (0.6)	4 (1.1)
Duration of Hospitalization Prior to Randomization		
<5 days	80 (22.1)	81 (22.3)
≥5 days	278 (76.8)	279 (76.6)
missing	4 (1.1)	4 (1.1)
Baseline LRT Pathogen Identified		
None identified	84 (32.1)	94 (25.8)
Monomicrobial	146 (40.3)	145 (39.8)
Polymicrobial	132 (36.5)	125 (34.3)
Region		
North America	15 (4.1)	16 (4.4)
Latin America	21 (5.8)	21 (5.8)
Western Europe[1]	53 (14.6)	52 (14.3)
Eastern Europe	231 (63.8)	232 (63.7)
Asia/Pacific	28 (7.7)	29 (8.0)
Rest of the World	14 (3.9)	14 (3.9)

[1] Data on race and/or ethnicity were not collected in France because of local regulations.
Source: Reviewer's analysis based on ADSL analysis dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Since subjects were hospitalized for IV administration of the study drug, compliance with the study drug regimen was high and similar between the treatment groups. Less than 1% of subjects were considered non-compliant with study drug regimen.

The majority (99.2%) of the subjects received at least 1 concomitant nonantibacterial medication. The most common classes of concomitant nonantibacterial medications were from the heparin group (enoxaparin or enoxaparin sodium and heparin), electrolyte solutions, and proton pump inhibitors. The use of various concomitant nonantibacterial medications was generally similar between treatment groups.

Overall, 58% of the subjects received concomitant non-study antibacterial medications during the study follow-up. A non-study antibacterial was an antibacterial other than the randomized treatments or the protocol allowed adjunctive therapies. Only 21% of the subjects in both treatment groups received a concomitant non-study antibacterial medication while on study drug therapy. Thus, the majority received the concomitant non-study antibacterial medications after discontinuing study drug. The most common concomitant non-study antibacterial medications received while on-study therapy were metronidazole, erythromycin, and vancomycin.

As previously mentioned, Gram-positive adjunctive therapy was required in all subjects at baseline and less than 5% of subjects did not receive Gram-positive adjunctive therapy as required by the protocol. Additionally, Gram-negative therapy was allowed at baseline to be given for a maximum of 72 hours at sites with a local prevalence of meropenem-resistant *P. aeruginosa* of at least 15%. Overall 30% of subjects received Gram-negative adjunctive therapy. Only 1 subject in each treatment group received Gram-negative adjunctive therapy for more than the 72 hours from baseline allowed by the protocol.

Table 16. Concomitant and Adjunctive Therapy Use- ITT Population

Therapy	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)
Concomitant nonantibacterial medication	361 (99.7)	359 (99.2)
Concomitant non-study nonantibacterial medication (during study)	218 (60.2)	205 (56.3)
Concomitant non-study nonantibacterial medication (while on study therapy)	77 (21.3)	78 (21.4)
Gram-positive adjunctive therapy	350 (96.7)	349 (95.9)
Gram-negative adjunctive therapy	103 (28.5)	112 (30.8)

Source: Adapted from Clinical Study Report Tables 14.1-31, 14.1-32, 14.1-59, 10-10, and 10-11.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was Day 28 all-cause mortality in the ITT population and the results are presented in Table 17. The Day 28 all-cause mortality rates were 24.0% for ceftolozane/tazobactam and 25.3% for meropenem. The mortality rate for meropenem is similar to the active control rates used to justify the noninferiority margin included in the HABP/VABP guidance. The stratified difference (meropenem - ceftolozane/tazobactam) in the mortality rates was 1.1% with a corresponding stratified 95% confidence interval for the difference of (-5.1%, 7.4%). Since the lower limit of the confidence interval is greater than the noninferiority margin of -10%, ceftolozane/tazobactam met the prespecified criteria for demonstrating noninferiority to meropenem. Survival status was unknown for only 3 subjects; all received meropenem. A sensitivity analysis treating these subjects as having survived was conducted and noninferiority of ceftolozane/tazobactam was still met.

Table 17. Day 28 All-Cause Mortality (ITT Population)

Mortality	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)	Difference (95% Confidence Interval)*
Overall	87/362 (24.0)	92/364 (25.3)	1.1 (-5.1, 7.4)
Diagnosis			
VABP	63/263 (24.0)	52/256 (20.3)	-3.6 (-10.7, 3.5)
vHABP	24/99 (24.2)	40/108 (37.0)	12.8 (0.2, 24.8)
Age Category			
<65 years	37/202 (18.3)	38/204 (18.6)	0.3 (-7.3, 7.9)
≥65 years	50/160 (31.3)	54/160 (33.8)	2.5 (-7.7, 12.6)

*The difference is calculated as meropenem – ceftolozane/tazobactam. For overall, the difference is the weighted proportion difference using Mehrotra-Railkar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method. For the individual strata raw differences and unstratified Newcombe confidence intervals are reported.
Sources: Reviewer conducted analyses and adapted from Clinical Study Report Table 11-1

Also presented in Table 17 are the Day 28 all-cause mortality results for the stratum subgroups (diagnosis and age). Overall, the results are generally consistent with the overall population and provide support of noninferiority of ceftolozane/tazobactam. In the vHABP subgroup, Day 28 all-cause mortality was lower in the ceftolozane/tazobactam group than the meropenem group. Although the confidence interval about the treatment difference excludes 0, statistical significance cannot be inferred as statistical control of type I error was not prespecified for this analysis. Furthermore, an assessment of baseline characteristics for the vHABP subgroup indicate that the meropenem vHABP subgroup may have been a sicker population than the ceftolozane/tazobactam vHABP subgroup which may in part explain the higher Day 28 all-cause mortality rate observed for the meropenem vHABP subgroup. The meropenem vHABP subgroup as compared to the ceftolozane/tazobactam vHABP subgroup contains numerically more subjects older than 65 years (56.5% vs 47.4%), with a baseline APACHE II score greater than or equal to 20 (37.4% vs 31.3%), and with a baseline diagnosis of congestive heart failure (24.3% vs 17.2%). Although the Day 28 all-cause mortality rates observed were numerically higher for the ≥65 years subgroup compared to the <65 years subgroup, the Day 28 all-cause mortality rates were similar between the treatment groups.

The results for the additional sensitivity analyses for Day 28 all-cause mortality are summarized in Table 18. The first sensitivity analysis is an overall unstratified analysis. One sensitivity analysis is based on the randomized strata. Overall, 26 ceftolozane/tazobactam subjects and 33 meropenem subjects were mis-stratified at randomization. Twenty-one (21) ceftolozane/tazobactam subjects and 19 meropenem subjects were stratified at randomization as having a diagnosis of vHABP but were determined to be VABP. Five (5) ceftolozane/tazobactam subjects and 13 meropenem subjects were stratified at randomization as having a diagnosis of VABP but were determined to be vHABP. A single meropenem subject was mistakenly stratified at randomization as ≥65 years but was actually <65 years. As previously mentioned forced assignment of a subject to a treatment arm was allowed when the subject was initially randomized to a study drug that was temporarily unavailable at the study site. This happened for 10 subjects in the ceftolozane/tazobactam subjects and 11 subjects in the meropenem arm. Therefore, a sensitivity analysis excluding these subjects was conducted. The results are robust for the various sensitivity analyses with all supporting non-inferiority of ceftolozane/tazobactam.

Table 18. Additional Sensitivity Analyses for Day 28 All-Cause Mortality (ITT Population)

	Ceftolozane/Tazobactam	Meropenem	Difference (95% Confidence Interval)*
Overall (unstratified)	87/362 (24.0)	92/364 (25.3)	1.3 (-5.0, 7.5)**
Based on randomized strata	87/362 (24.0)	92/364 (25.3)	1.1 (-5.2, 7.3)
Excluding forced randomized subjects	84/352 (23.9)	91/353 (25.8)	1.8 (-4.6, 8.2)

*The difference is calculated as meropenem – ceftolozane/tazobactam.
**Unstratified Newcombe confidence interval about the difference reported.
***The difference is the weighted proportion difference using Mehrotra-Railkar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method.
Sources: Reviewer conducted analyses and adapted from Clinical Study Report Table 11-3

The results of Day 28 all-cause mortality for various subgroups are summarized in Table 19. In general, the results within subgroups are consistent with the overall population. As would be expected, subjects with poorer prognostic factors at baseline (such as renal impairment, APCAHE II score ≥ 20, and bacteremia) had higher Day 28 all-cause mortality rates but this was observed in both treatment groups. However, the interpretation of the results should be made with caution due small sample sizes in many of the subgroups and the lack of type I error control for multiple comparisons.

Table 19. Day 28 All-Cause Mortality by Various Subgroups (ITT Population)

	Ceftolozane/Tazobactam	Meropenem	Difference (95% CI)*
Gender			
Male	57/262 (21.8)	60/255 (23.5)	1.8 (-5.4, 9.0)
Female	30/100 (30.0)	32/109 (29.4)	-0.6 (-13.0, 11.6)
Race			
White	72/301 (23.9)	76/300 (25.3)	1.4 (-5.5, 8.3)
Non-White	11/42 (26.2)	9/35 (25.7)	-0.5 (-20.2, 19.2)
Not Reported	4/19 (21.1)	7/29 (24.1)	3.0 (-21.1, 27.1)
Region			
North America	3/15 (20.0)	2/16 (12.5)	-7.5 (-34.3, 19.4)
Latin America	7/21 (33.3)	8/21 (38.1)	4.8 (-22.7, 31.3)
Western Europe	10/53 (18.9)	12/52 (23.1)	4.2 (-11.4, 19.7)
Eastern Europe	57/231 (24.7)	61/232 (26.3)	1.6 (-6.3, 9.5)
Asia/Pacific	8/28 (28.6)	7/29 (24.1)	-4.4 (-26.4, 17.9)
Rest of the World	2/14 (14.3)	2/14 (14.3)	0.0 (-27.6, 27.6)
Baseline Creatinine Clearance (mL/min)			
≥150 (hyperclearance)	10/67 (14.9)	7/64 (10.9)	-4.0 (-15.8, 8.0)
≥80 to <150 (normal)	30/160 (18.8)	38/172 (22.1)	3.3 (-21.1, 27.1)
>50 to <80 (mild impairment)	30/82 (36.6)	22/77 (28.6)	-8.0 (-22.0, 6.5)
≥30 to ≤50 (moderate impairment)	11/35 (31.4)	10/26 (38.5)	7.0 (-16.0, 30.0)
≥15 to <30 (severe impairment)	6/17 (35.3)	13/21 (61.9)	26.6 (-4.9, 51.6)
<15 (ESRD)	-	1/1 (100.0)	NA
>50	70/309 (22.7)	67/313 (21.4)	-1.3 (-8.0, -5.5)
≤50	17/52 (32.7)	24/48 (50.0)	17.3 (-3.7, 38.3)
Baseline APACHE II Score			
<20	45/237 (19.0)	53/247 (21.5)	2.5 (-4.7, 9.6)
≥20	42/124 (33.9)	38/115 (33.0)	-0.8 (-12.6, 11.1)
Bacteremic at Baseline			
Yes	23/64 (35.9)	13/41 (31.7)	-4.2 (-21.5, 14.4)
No	64/298 (21.5)	79/323 (24.5)	3.0 (-3.7, 9.5)
Prior Antibiotic Use			
Yes	71/318 (22.3)	83/323 (25.7)	3.4 (-3.3, 9.9)
No	16/44 (36.4)	9/41 (22.0)	-14.4 (-32.2, 5.0)
Prior Gram-negative Antibacterial Use	51/190 (26.8)	61/193 (31.6)	4.8 (-4.3, 13.8)
>24 hours	16/95 (16.8)	17/95 (17.9)	1.1 (-9.8, 11.9)
≤24 hours	20/77 (26.0)	14/76 (18.4)	-7.6 (-20.5, 5.7)
None			
Failure of Prior Antibacterial Therapy for HABP/VABP			
Yes	12/53 (22.6)	18/40 (45.0)	22.4 (3.1, 40.1)
No	75/309 (24.3)	74/323 (22.9)	-1.4 (-8.0, 5.2)
Number of Baseline Pathogens			
Monomicrobial	30/146 (20.5)	36/145 (24.8)	4.3 (-5.3, 13.8)
Polymicrobial	27/132 (20.5)	30/125 (24.0)	3.5 (-6.6, 13.7)
Gram-negative pathogens only	16/71 (22.5)	15/59 (25.4)	2.9 (-11.5, 17.7)
Gram-negative and Gram-positive	11/60 (18.3)	15/64 (23.4)	5.1 (-9.4, 19.2)
Gram-positive only	0/1	0/2	N/A

* Difference is meropenem – ceftolozane/tazobactam.
Source: Reviewer conducted analyses and adapted from Clinical Study Report Table 11-9 and Table 1 of response to information request dated 4/22/19

Efficacy Results – Secondary and other relevant endpoints

Clinical response (cure) at the TOC visit was a key secondary endpoint. Overall, the clinical cure rate at the TOC visit was 54.4% in the ceftolozane/tazobactam group compared to 53.3% in the meropenem group. The protocol specified noninferiority margin was 12.5%, however a data driven justification of a margin for clinical cure has not been established. Regardless, the confidence interval rules out an absolute reduction in the clinical cure rate of more than 6%. The results for the stratification factors are generally consistent with those observed overall and the confidence intervals rule out an absolute reduction in clinical cure rate of more than 10%. Sensitivity analyses based on randomized stratum and by excluding forced randomized subjects (data not shown) are also consistent with the overall results.

Table 20. Clinical Response (Cure) at TOC (ITT Population)

Clinical Response	Ceftolozane/Tazobactam (n=362)	Meropenem (n=364)	Difference (95% Confidence Interval)*
Overall			
Cure	197 (54.4)	194 (53.3)	1.1 (-6.2, 8.3)
Failure	105 (29.0)	97 (26.7)	
Indeterminate	60 (16.6)	73 (20.0)	
Diagnosis			
VABP	147/263 (55.9)	146/256 (57.0)	-1.1 (-9.6, 7.4)
vHABP	50/99 (50.5)	48/108 (44.4)	6.1 (-7.4, 19.3)
Age Category			
<65 years	121/202 (59.9)	118/204 (57.8)	2.1 (-7.5, 1.5)
≥65 years	76/160 (47.5)	76/160 (47.5)	0.0 (-10.8, 10.8)

* The difference is calculated as ceftolozane/tazobactam- meropenem). For overall, the difference is the weighted proportion difference using Mehrotra-Railkar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method. For the individual strata raw differences and unstratified Newcombe confidence intervals are reported.
Source: Reviewer conducted analyses and adapted from Clinical Study Report Table 11-2

The HABP/VABP guidance recommends limiting the enrollment of subjects to those who received no more than 24 hours of prior antibacterial therapy. In the seriously ill population enrolled in this study, approximately 53% of subjects received more than 24 hours of a prior non-study systemic Gram-negative antibacterial. Also, as previously discussed, approximately 30% of subjects received up to 72 hours adjunctive Gram-negative antibacterial therapy per the protocol. To allow for the least confounded assessment of the effect of randomized therapy, a sensitivity analysis on the subset of subjects who received no or ≤24 hours of a prior systemic Gram-negative antibacterial therapy and no adjunctive Gram-negative therapy was conducted (Table 21). Given the reduced sample size, the confidence intervals about the treatment difference are wider than those for the overall population. However, the results generally support non-inferiority of ceftolozane/tazobactam.

Table 21. Day 28 All-Cause Mortality and Clinical Cure at TOC Visit for Subset of Subjects Who Received No/≤24 Hours of Prior Systemic Gram-Negative Antibacterial Therapy and No Adjunctive Gram-Negative Therapy

Day 28 All-Cause Mortality		Clinical Cure at TOC Visit	
Ceftolozane/Tazobactam	**Meropenem**	**Ceftolozane/Tazobactam**	**Meropenem**
25/134 (18.7)	20/126 (15.9)	84/134 (62.7)	71/126 (56.3)
-2.8 (-12.0, 6.5)*		6.3 (-5.5, 18.0)**	

*Difference is calculated as meropenem- ceftolozane/tazobactam
**Difference is calculated as ceftolozane/tazobactam- meropenem
The difference is the weighted proportion difference using Mehrotra-Rai kar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method.
Source: Reviewer conducted analyses and adapted from Tables 3 and 4 of response to information request dated 1/9/19

Analyses of Day 28 all-cause mortality and clinical response at the TOC visit were also conducted using the mITT population. These results are summarized in Table 22 along with the results for selected baseline pathogens. Overall for the mITT population, the Day 28 all-cause mortality rates and clinical cure rates were similar between the treatment arms and consistent with that observed in the ITT population.

Table 22. Day 28 All-Cause Mortality and Clinical Cure Rates at the TOC Visit for the mITT (protocol-defined) Population and by Select Baseline Pathogens

	Day 28 All-Cause Mortality		Clinical Cure at TOC Visit	
	Ceftolozane/ Tazobactam	**Meropenem**	**Ceftolozane/ Tazobactam**	**Meropenem**
Overall, mITT	53/264 (20.1)	63/247 (25.5)	160/264 (60.6)	140/247 (56.7)
	4.4 (-2.8, 11.8)*		2.7 (-5.9, 11.2)**	
Baseline Pathogen				
Pseudomonas aeruginosa	16/63 (25.4)	12/65 (18.5)	36/63 (57.1)	39/65 (60.0)
Enterobacteriaceae	38/195 (19.5)	49/185 (26.5)	120/195 (61.5)	105/185 (56.8)
Enterobacter cloacae	2/17 (11.8)	10/16 (62.5)	10/17 (58.8)	4/16 (25.0)
Escherichia coli	11/51 (21.6)	11/42 (26.2)	32/51 (62.7)	26/42 (61.9)
Klebsiella (Enterobacter) aerogenes	1/8 (12.5)	3/8 (37.5)	4/8 (50.0)	3/8 (37.5)
Klebsiella oxytoca	3/14 (21.4)	3/12 (25.0)	9/14 (64.3)	7/12 (58.3)
Klebsiella pneumoniae	19/86 (22.1)	19/91 (20.9)	53/86 (61.6)	58/91 (63.7)
Proteus mirabilis	5/24 (20.8)	7/20 (35.0)	13/24 (54.2)	11/20 (55.0)
Serratia marcescens	6/18 (33.3)	1/12 (8.3)	9/18 (50.0)	7/12 (58.3)
Haemophilus influenzae	0/22 (0)	2/16 (12.5)	19/22 (86.4)	8/16 (50.0)

* Difference is calculated as meropenem- ceftolozane/tazobactam
** Difference is calculated as ceftolozane/tazobactam- meropenem
The difference is the weighted proportion difference using Mehrotra-Rai kar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method.
Source: Reviewer conducted analyses and adapted from Clinical Study Report Tables 11-11 and 14.2-19

The mITT population was defined in the protocol to include subjects who had a baseline pathogen susceptible to at least one of the study drugs. Typically for a noninferiority study, the definition would be based on baseline pathogens susceptible to the control arm to ensure that comparisons are made to an effective control. Since the primary analysis population for this study was the ITT population, this difference in the definition of the mITT population is less of an issue. Nonetheless, sensitivity analyses were conducted in the subset of the mITT population that had all baseline pathogens that were susceptible to meropenem without regard to the randomized study treatment and for the subset of the mITT population that had baseline pathogens susceptible to both study drugs. The results for these sensitivity analyses are summarized in Table 23 and are consistent with those observed for the protocol defined mITT population.

Table 23. Sensitivity Analyses of Day 28 All-Cause Mortality and Clinical Cure at TOC Visit by Various Baseline Pathogen Susceptibly Requirements (mITT Population)

	Day 28 All-Cause Mortality		Clinical Cure at TOC Visit	
	Ceftolozane/Tazobactam	**Meropenem**	**Ceftolozane/Tazobactam**	**Meropenem**
Baseline Pathogens Susceptible to Meropenem	46/237 (19.4)	56/219 (25.6)	150/237 (63.3)	126/219 (57.5)
	4.9 (-2.7, 12.6)*		4.7 (-4.3, 13.6)**	
Baseline Pathogens Susceptible to Both Study Treatments	29/190 (15.3)	46/185 (24.9)	127/190 (66.8)	107/185 (57.8)
	8.6 (0.6, 16.6)*		8.1 (0-1.7, 17.8)**	

* Difference is calculated as meropenem- ceftolozane/tazobactam
** Difference is calculated as ceftolozane/tazobactam- meropenem
The difference is the weighted proportion difference using Mehrotra-Rai kar continuity correct minimum risk stratum weight for the strata of diagnosis and age categories and the 95% confidence interval is based on the stratified Newcombe method.
Source: Reviewer conducted analyses and adapted from Tables 1 and 2 of response to information request dated 1/9/19

Table 24 summarizes the by-pathogen rates of Day 28 all-cause mortality and clinical response at the TOC visit in the subset where the respective baseline pathogen was susceptible to meropenem. As all *Enterobacter cloacae*, *Escherichia coli*, and *Klebsiella oxytoca* were susceptible to meropenem, the results for these pathogens are the same as those presented in Table 22.

Table 24: By Pathogen Analysis of Day 28 All-Cause Mortality and Clinical Response at TOC Visit where Pathogen is Susceptible to Meropenem

	Day 28 All-Cause Mortality		Clinical Cure at TOC Visit	
Baseline Pathogen	**Ceftolozane/ Tazobactam**	**Meropenem**	**Ceftolozane/ Tazobactam**	**Meropenem**
Pseudomonas aeruginosa	14/50 (28.0)	10/56 (17.9)	30/50 (60.0)	34/56 (60.7)
Enterobacteriaceae	36/192 (18.8)	49/182 (26.9)	119/192 (62.0)	102/182 (56.0)
Enterobacter cloacae	2/17 (11.8)	10/16 (62.5)	10/17 (58.8)	4/16 (25.0)
Escherichia coli	11/51 (21.6)	11/42 (26.2)	32/51 (62.7)	26/42 (61.9)
Klebsiella (Enterobacter) aerogenes	0/6 (0)	3/7 (42.9)	3/6 (50.0)	2/7 (28.6)
Klebsiella oxytoca	3/14 (21.4)	3/12 (25.0)	9/14 (64.3)	7/12 (58.3)
Klebsiella pneumoniae	19/85 (22.4)	19/90 (21.1)	52/85 (61.2)	57/90 (63.3)
Proteus mirabilis	5/23 (21.7)	7/20 (35.0)	13/23 (56.5)	11/20 (55.0)
Serratia marcescens	5/17 (29.4)	1/12 (8.3)	9/17 (52.9)	7/12 (58.3)
Haemophilus influenzae	0/20 (0)	2/15 (13.3)	17/20 (85.0)	8/15 (53.3)

Source: Adapted from Tables 1 and 2 of response to information request dated 5/9/19

8.1.3. Integrated Assessment of Effectiveness

The pivotal evidence to support the efficacy of ceftolozane/tazobactam for the treatment of VABP/vHABP was the single Phase 3 trial PN008. A single Phase 3 trial was accepted to provide evidence of effectiveness for efficacy of ceftolozane/tazobactam for the treatment of VABP/vHABP since ceftolozane/tazobactam is already approved for 2 other infectious disease indications: complicated intra-abdominal infections and complicated urinary tract infections. Additional supportive information was provided by in vitro studies and animal models of infection.

The results of PN008 demonstrate noninferiority of ceftolozane/tazobactam to meropenem in the Day 28 all-cause mortality rate. Results for the key secondary endpoint of clinical response at the TOC visit showed similar results for the two treatment arms. The results were robust to various subgroup and sensitivity analyses. One limitation to the generalizability of the results is the lack of ethnic and racial diversity due to the enrollment of sites primarily in Eastern Europe.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of ceftolozane/tazobactam has been reported for the cIAI and cUTI indications. The current review focuses on safety findings for Study PN008 with respect to the HABP/VABP

indication.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 361 subjects received ceftolozane/tazobactam (TOL/TAZ) at the proposed marketed dose of 3 g q8h in the pivotal Phase 3 study (PN008). In the Phase 1 studies, 71 subjects were exposed to a 3 g (or CrCL-adjusted) dose of TOL/TAZ, of whom 37 received a single dose and 34 received multiple (up to 28) doses.

Table 25. Overall Extent of Exposure

Safety Database for the Study Drug[1]		
Clinical Trial Groups	Ceftolozane/Tazobactam (n= 361)	Meropenem (n=359)
Controlled trial conducted for this indication, PN008[2]	n= 361	n=359
Phase 1 trials conducted to support 3g Q8h dose	n=71 (35 healthy/36 patients)	
Duration of Exposure in Subjects in Phase 1 trials (Total N=71)		
Number of doses	Treatment	Control
Single dose	n=37 (27 healthy and 10 patients)	
Multiple dose (28 doses)	ceftolozane/tazobactam 1.5g Q8h n=8 (healthy)	N=4 (Placebo)
Multiple doses (4 to 6 doses)	ceftolozane/tazobactam[3] 3g Q8h, n=26 (patients)	

[1] *Study drug* means the drug being considered for approval for this indication. Individuals exposed to the study drug, for the indication under review, N=432.
[2] To be used in product's labeling. 3: dose and schedule were adjusted according to CrCl

Exposure in the controlled trial to support this indication, PN008

A total of 225 of 361 (62.3%) patients in the ceftolozane/tazobactam arm and 224 of 359 (62.3%) in the meropenem arm received between 8 and 14 days of therapy, which is the proposed duration of treatment for the indication sought. Table 26 below shows duration of exposure by calendar days of treatment in the safety population.

Table 26. Study Drug Exposure in PN008 (Safety Population)

	Ceftolozane/Tazobactam N=361	Meropenem N=359
Days of Treatment	**N (%)**	**N** (%)
1 to 2	10 (2.8%)	18 (5%)
3	20 (5.5%)	10 (2.8%)
4 to 6	37 (10%)	68 (19%)
7	11 (3.0)	4 (1.1)
8	11(3.0)	12 (3.3)
9	163 (45.2)	156 (43.5)
10-13	39 (10.8)	41 (11.4)
14	12 (3.3%)	15 (4.2%)
15	56 (3.3%)	61(4.2%)
>15	0	0
Duration of Exposure: Study Days		
Statistic	Ceftolozane/tazobactam	Meropenem
N	361	359
Mean (SD)	8.00 (3.532)	8.23 (3.609)
Median	7.70	7.70
Min., Max.	0.3, 13.8	0.0, 13.8

Source: Table 10-13 from the CSR

Adequacy of the safety database

The dosing, duration, and number of subjects in the safety database are sufficient to conduct a safety review for the HABP/VABP indication. Assessments in the database are recorded from the first dose of study to the final assessment for mortality (occurring on study day 28 to 32 post-randomization).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no significant concerns regarding data integrity, please refer to Section 4.1 for details on selected sites for inspection. The frequency and type of adverse event collection and monitoring were appropriate to evaluate the product's safety in this patient population. Regarding the quality of the data for safety assessment, there were some limitations noted in the data fitness assessment conducted by the JumpStart team, Office of Computational Science, CDER. These were individually reviewed by the Clinical reviewer. The quality of the coding was reviewed by the Clinical reviewer, particularly focusing on the MedDRA PTs and comparing them to the corresponding lower level terms. There were no incorrect or misleading translations of lower level terms, therefore there was no need to reclassify any preferred terms. After information requests were sent to the Applicant, the most relevant issues were resolved with satisfactory responses. Of note, 38% of laboratory results were missing upper limit of normal (ULN) parameters. A thorough review of these revealed that these included values from the blood count differential (lymphocytes, eosinophils, basophils), which did not significantly

affect the evaluation of the safety endpoints. Regarding chemistry laboratory values, a total of 247 Zerbaxa and 244 meropenem patients had at least one reported creatinine value without a corresponding upper limit of normal parameter. All of these cases were from local lab results that were collected at unscheduled visits, which did not impair the ability to review the data.

Categorization of Adverse Events

Adverse event definitions were in accordance with CFR and ICH guidelines. Adverse events were categorized according the MedDRA hierarchy, version 17, and their severity evaluation followed commonly used WHO guidelines (mild, moderate, severe). In addition, toxicity grades were calculated using the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (November 2007).

The Applicant conducted a post-hoc safety analysis to evaluate the magnitude of treatment emergent adverse events (TEAEs) and associated confidence intervals (CI) for the risk differences between treatment arms for the AE categories (any TEAEs, SAEs, TEAEs leading to death or to discontinuation of the study drug).

Routine Clinical Tests

Routine safety assessments were conducted at pre-specified time points throughout the clinical trial: daily during treatment (Days 1 to 14), at EOT (within 24 hours of last dose), at TOC (7 to 14 days after last dose) and at LFU, as well as unscheduled and as needed. Study assessments included incidence, severity and relatedness of AEs, SAEs, incidence and relatedness of deaths, vital signs and physical examination findings. Laboratory assessments included clinical chemistry, hematology, direct Coombs testing, and microbiology assessments, such as blood culture and respiratory cultures at baseline and as clinically indicated during follow-up.

8.2.4. Safety Results

Table 27. Overview of Treatment Emergent Adverse Events

Adverse Event Category	Ceftolozane/Tazobactam N=361 N (%)	Meropenem N=359 N (%)
Subjects with any TEAE	310 (85.9)	299 (83.3)
Number of subjects with any serious TEAE	153 (42.4)	129 (36.0)
Number of subjects with any TEAE leading to discontinuation of study drug treatment	37 (10.2)	42 (11.7)
Number of subjects with any TEAE leading to discontinuation of study*	107 (29.6)	99 (27.2)
Number of subjects with any TEAE which resulted in death	105 (29.1)	101 (28.1)

* Includes TEAE with an outcome of death.
Source: ADSL, ADAE, Applicant's Treatment Emergent flag in the ADAE dataset applied. From Applicant's Table 14.3-1 of the CSR.

8.2.4.1. Deaths

Deaths up to Day 28 represent the primary efficacy endpoint. This section will review all deaths that occurred during the study, especially those that were reported as fatal outcomes of TEAEs. The table below shows all deaths that occurred during the study. No unreported deaths were found in a thorough search of the databases by the JumpStart team, OCS. There were 209 deaths in the study, of which 208 were in the safety population and one in an untreated subject. The distribution of deaths was not clustered around sites, geographical region or demographic group, and there were no significant differences between treatment arms in the distribution of deaths by demographic characteristics. Please refer to Table 28 below. In both arms, the proportion of deaths in females was relatively higher (by approximately 6%) than that in men, a similar difference observed in both treatment arms. However, there was a higher percentage of males enrolled in the study (71% males vs. 29% females) with similar proportions in both treatment arms, and the comparisons by gender have limitations because of the differences in group size. As expected, a higher proportion of deaths was observed in patients older than 65 years (by approximately 18%) than in the younger-than 65-year-old age group, and the proportions were similar in both treatment and comparator arms. The mortality rate in the subgroup of patients with ventilated HABP (vHABP) was higher in both treatment arms as compared with the corresponding treatment arms for VABP patients. This finding is consistent with another published study of hospital-acquired pneumonia that included ventilated HABP and VABP patients (Talbot et al. 2019). While in the ceftolozane/tazobactam (TOL/TAZ) arm, the mortality rate difference between ventilated HABP (31.3% mortality) and VABP (28.2% mortality) was 3%, this difference was more pronounced in the meropenem (control) treatment

arm, with a 16% higher mortality rate in the ventilated HABP arm (39% mortality) as compared to the VABP arm (23.6% mortality). In response to our inquiry, the Applicant responded that the redistribution of initially incorrectly classified meropenem subjects from the vHABP group to the VABP category (done prior to unblinding) may have contributed to the higher mortality rate seen in the meropenem treated vHABP subjects. A review of baseline characteristics of patients by the corrected stratification group revealed the following differences that were proportionately higher in the meropenem vHABP as compared to the corresponding stratum of the TOL/TAZ arm: a 10% higher proportion of patients with APACHE score >20, a 6% higher proportion of patients above 65 years of age, a 9% higher proportion of congestive heart failure and a higher proportion of patients who received 2 days or less of treatment (8.4% vs 4.0%). Likewise, in the VABP arm, baseline differences showed an opposite trend, with higher proportions of patients with the following baseline risk factors in the TOL/TAZ arm as compared to the meropenem arm: a 6.5% higher proportion of patients with APACHE score of 20 or higher, an 8% higher rate of patients with bacteremia, and an 8% higher proportion of patients with diabetes.

Stratification by diagnosis was included in the design to ensure a balance of subjects by diagnosis in each treatment arm. The vHABP stratum was smaller than the VABP group, and differences in mortality rates may reflect not only the differences in baseline risk factors but also the relatively small sample size of this stratum.

Table 28. Deaths Summary: Number of Reported Patient Deaths and Potentially Unreported Deaths by Actual Arm

Actual Arm	Reported Subject Deaths	Potentially Unreported Deaths
Not treated	1	0
Ceftolozane/tazobactam	106	0
Meropenem	102	0
Totals	209	0

Detailed death information for each subject by dataset was searched and reviewed. This information was found by searching all SDTM datasets for terms associated with death (e.g., death, fatal, dead, died, autopsy, “dth”). Potentially unreported deaths would be those found somewhere in the data, but not reported in DM or DS.

Table 29. Distribution of Fatal TEAEs by Stratification Factors and Demographic Characteristics

	Treatment		Control	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Safety subgroup (TRTEMFL = 'Y', AESDTH = 'Y')	105* (29.1)	361	101 (28.1)	359
Sex				
Female	34 (34.0)	100	35 (32.7)	107
Male	71 (27.2)	261	66 (26.2)	252
Age group				
Age group 1 (Age <65)	43 (21.4)	201	40 (19.8)	202
Age group 2 (Age ≥65)	62 (38.8)	160	61 (38.9)	157

	Treatment		Control	
Subgroup	**n (%)**	**N**	**n (%)**	**N**
Race				
American Indian or Alaska Native	0	0	1 (100.0)	1
Asian	9 (33.3)	27	6 (26.1)	23
Black or African American	2 (20.0)	10	1 (25.0)	4
Missing	0	0	1 (50.0)	2
Native Hawaiian or other Pacific Islander	0 (0.0)	1	0	0
Other	6 (26.1)	23	8 (25.0)	32
White	88 (29.3)	300	84 (28.3)	297
Ethnicity				
Hispanic or Latino	9 (37.5)	24	8 (33.3)	24
Missing	6 (18.8)	32	15 (25.4)	59
Not Hispanic or Latino	90 (29.5)	305	78 (28.3)	276
Region				
Africa	1 (16.7)	6	0 (0.0)	6
Asia	21 (35.0)	60	17 (27.9)	61
Europe	71 (27.8)	255	71 (28.4)	250
Other	0 (0.0)	4	2 (33.3)	6
South America	8 (38.1)	21	8 (38.1)	21
United States	4 (26.7)	15	3 (20.0)	15
Primary diagnosis (STRAT1)				
VABP	74 (28.2)	262	60 (23.6)	254
Ventilated HABP	31 (31.3)	99	41 (39.0)	105

*The treatment emergent flag was missing in one patient in the TOL/TAZ arm (CXA-NP-11-04-2404-1091), who had received treatment for 3 days.

The Applicant presented the fatal AEs by SOC and by PT in Table 12.4 of the CSR and discussed the events by order of frequency based on the total incidence of events in the whole study population. A review of the deaths by order of frequency in the treatment arm is presented in the table below (Clinical reviewer table, Table 30).

The SOC with the highest number of deaths in the treatment arm was nervous system disorders (24/361 or 6.6% vs 19/359 or 5.3% in the TOL/TAZ vs. meropenem arms, respectively). The PTs within this SOC reflected predominantly cerebrovascular hemorrhagic events. A review of these events with broad and narrow SMQs identified 16/361 (4.4%) fatal events in the TOL/TAZ arm and 4/359 (1.1%) in the meropenem arm, representing the highest risk difference among fatal events. These cases were individually reviewed, and additional information was requested from the Applicant. Initially, a total of 24 patients were identified with worsening cerebrovascular events in the study, 18 in the TOL/TAZ arm and 6 in the meropenem arm. Later, one of the TOL/TAZ patients was found to have experienced an ischemic stroke without hemorrhagic conversion (Subject (b) (6)), therefore the total number of subjects with worsening or recurrent cerebrovascular events, mostly intracranial hemorrhages was 23 (17 in the TOL/TAZ arm and 6 in the meropenem arm). In 16 of the 17 patients in the TOL/TAZ arm and in 5 of 6 the patients in the meropenem arm, worsening or recurring hemorrhage was confirmed and reported. Regarding the other two patients, one in the TOL/TAZ arm ((b) (6)) had brain herniation after a parietal fracture after severe trauma, and one patient in the meropenem arm ((b) (6)), had brain herniation after a cerebrovascular event, along with gastrointestinal bleeding. These two patients had brain herniation without specific mention of CNS hemorrhage

or of an alternative cause for the brain herniation. In these patients, because of the history of their disease and risk factors, intracranial hemorrhage is a possible cause of brain herniation, but it was not specifically mentioned in the data submitted. Therefore, the number of confirmed worsening or recurrent intracranial hemorrhage patients is 16 in the TOL/TAZ arm and 5 in the meropenem arm. For more details about these patients, please refer to Appendix 19.5. The original 23 subjects had medical histories related to either cerebral bleeding/injury (79.2%) or cerebral ischemia (16.7%) prior to entering the study. Among most of these patients, there were no significant changes in coagulation parameters or platelet counts during the study. Besides hypertension, present in 7 of 17 and 5 of 6 patients in the treatment and comparator arms, respectively, no other apparent differences in risk factors for bleeding (liver disease, coagulopathies or anticoagulant treatment) were noted among these patients.

Only one of the 23 patients had another type of bleeding concomitantly (gastrointestinal bleeding). This patient (# (b) (6), TOL/TAZ arm) had received full anticoagulation, on the day before the event, which occurred at Day 6, to treat pulmonary thromboembolism. In the meropenem arm, one patient (# (b) (6)) was receiving heparin anticoagulation for treatment of humeral and ulnar vein thrombosis, and another patient (# (b) (6)) had thrombocytopenia on Days 3 and 4, before the event. Other contributing factors potentially affecting hemostasis were present in these 23 patients, although these were not present in all patients. For example, in the TOL/TAZ arm, one patient had renal failure (# (b) (6)), another had hepatic failure (# (b) (6)), and another had transient thrombocytopenia (# (b) (6)). There were no meaningful differences in concomitant medications in these 23 patients as compared to the rest of the study population. Almost half of the CNS bleeding events (45.8%) were reported in subjects who had ongoing CNS bleed events at baseline prior to the first dose of study drug, and they had worsened or recurred during the study. The median day of occurrence of intracranial bleeding events was Day 6 in the treatment arm and Day 10 in the comparator arm, with a range of Days 1 to 35 in the treatment arm, and Days 5 to 21 in the comparator arm. Patients in the TOL/TAZ arm had a median of 7 days of treatment, with a range of 1 to 15 days. Meropenem recipients had a median of 8 days of treatment. In 8 TOL/TAZ patients and 2 meropenem patients, the events occurred during treatment. Of the 8 TOL/TAZ patients who had events after treatment, 4 had events between 1 and 4 days after the last dose, and 4 between 7 and 26 days after last dose. In the meropenem arm, 3 patients had events after treatment, between 2 and 11 days after the last dose. The median age was 52 years in meropenem and 57.5 years in TOL/TAZ arm. The gender distribution was similar to the gender proportions of the study population. Considering only the patients who had worsening of an intracranial hemorrhage during treatment, there were a total of 8 patients in TOL/TAZ and 2 in meropenem arm.

The proportion of patients enrolled in the study with a medical history of “central nervous system hemorrhages and cerebrovascular accidents” (MedDRA high level term) was 3% higher in the treatment arm (42% and 39%, in treatment and comparator arm, respectively). There was a 4% higher percentage of patients with a history of “cerebral injuries NEC” (MedDRA high level term) (20% and 16%, in treatment and comparator arms, respectively) and a 6% higher percentage of patients with diabetes (18% and 12%, respectively) in the treatment arm as compared with the comparator arm. These relatively small imbalances at baseline may have played some role in the differences observed in bleeding events, however, it is not possible to

rule out a potential contribution of the study drug to these events because of the high-risk difference observed in the rates (three-fold difference), the strong temporal association with treatment, and the biological plausibility. Elderly age (80 years and above) and hypertension are consistently reported and validated risk factors for both primary and recurrent intracranial hemorrhage events. In the TOL/TAZ arm, 45 of 361 (12.5%) patients were aged 80 years or older, and 33 of 359 (9.2%) were of that same age group in meropenem. Hypertension was reported by 209 (57.9%) of patients in TOL/TAZ arm and by 200 (55.7%) of meropenem patients as a condition noted in medical history. These differences were not substantial or proportional to the differences in outcomes of worsening or recurrent intracranial hemorrhages observed among treatment arms.

Findings regarding other potential predictors of recurrent intracranial hemorrhagic events among co-morbid diseases and use of antithrombotic treatment have yielded variable results and are not widely accepted. Beta-lactams, including piperacillin-tazobactam, penicillin, nafcillin and some cephalosporins, may cause bleeding by several mechanisms and including platelet aggregation dysfunction, causing alterations in hemostasis (Sattler et al. 1988). The consequences of this alteration vary in severity depending on the site and magnitude of the hemorrhage. The mechanism of this effect appears to be the irreversible binding of the beta-lactam to the platelets surface (Burroughs and Johnson 1990). The effect seems to be dependent on the dose and exposure duration. Recovery of platelet function can take up to 21 days, the time it takes to naturally replace platelets that are irreversibly bound to the drug. The platelet aggregation defect can be present with normal platelet counts and prothrombin time. It is plausible that TOL/TAZ, either of its components or tazobactam alone, may increase the risk of intracranial bleeding by inducing platelet dysfunction, inhibiting platelet aggregation. Piperacillin has been shown to inhibit platelet aggregation in healthy volunteers (Gentry et al. 1981) and in patients (Fass et al. 1987). Platelet dysfunction was not assessed in these patients or as a routine measurement during the study. It has been reported before that beta-lactams, including piperacillin alone or with tazobactam can induce platelet dysfunction without thrombocytopenia or increased prothrombin time and increase the risk of intracranial bleeding in patients (Fass et al. 1987; Bower et al. 2018). Platelet dysfunction is detected only by appropriately measuring bleeding time.

An overall 2% higher rate of hemorrhages in any anatomical site (with the SMQ “hemorrhages excluding laboratory terms”, not restricted to fatal events) was also observed in the TOL/TAZ arm in this study. Neither ceftolozane nor tazobactam contain the NMTT group, nor the HTT, TDT or MTDT group that have been associated with the issue of increased risk of bleeding due to hypoprothrombinemia (Chen et al. 2016), and there is no evidence of a mechanism of bleeding such as thrombocytopenia or coagulation abnormalities measured by PT/PTT. However, platelet dysfunction, only evident by measurement of bleeding time has not been assessed in these patients or in any during the study. Therefore, it is not possible to rule out the potential contribution of TOL/TAZ to the increased risk of intracranial bleeding.

A review of the available preclinical data did not suggest a potential higher risk of bleeding with the use of TOL/TAZ. Please refer to Section 5.2 for details of the coagulation studies conducted in rats and dogs. A FAERS database search was performed, which detected seven cases of

bleeding. The small number of cases and the lack of details in the reports preclude any definitive conclusion. Based on the available evidence, the risk of worsening intracranial bleeding may vary among patients and may likely be additive or higher in those with predisposing factors and/or concomitant medications or conditions known to increase the risk of bleeding. Two hematology consultants reviewed the 24 cases of suspected intracranial hemorrhage at the request of the Applicant. The consultants were asked if, with the information provided by Merck, any potential coagulopathy induced by study drugs could be identified that may explain the central nervous system complications. A summary of the consult responses is presented below.

Consult review by (b) (4):

(b) (4) stated that he reviewed the protocol synopsis, the FDA comments letter, selected pages from a document entitled, "ICH_AE_Subjects_Full Safety Narrative_ASPECT-NP_zerbaxa", and intracranial hemorrhage follow-up forms. He cited two review articles which described the risk of hemorrhagic transformation of ischemic stroke as high as 71% in autopsy studies and ranging from 13 to 43% in studies based on CT scans. The incidence of symptomatic hemorrhagic transformation ranges from 0.6 to 20% (Zhang et al. 2014). Increasing the size of the infarct increases the risk of hemorrhagic transformation. The risk of ICH recurrence after initial ICH varies by study and ranges from 0 to 24% (reviewed in Hanger et al. (2007)).

(b) (4) listed the potential mechanisms of drug-induced coagulopathy as:

1- Direct interference of production of vitamin K-dependent factors by the methylthiotetrazole (MTT) side chain
2- Inducing a vitamin K deficiency by altering coliform bacteria
3- Idiosyncratic reactions resulting in thrombocytopenia
4- Direct inhibition of platelet function

He explained that #1 and 2 would be detectable by prolongation of the prothrombin time (INR) and #3 by platelet counts, while #4 requires complex platelet function tests.
After summarizing the events by type and treatment arm, noting the timing and additional risk factors present, (b) (4) presented the following conclusions:

Figure 3. Conclusions of (b) (4) Regarding Drug-Induced Coagulopathy

Conclusions and limitations:

1) There was no obvious consistent coagulopathy based on the laboratory data provided. The observed abnormalities had reasonable explanations related to underlying diseases e.g. liver disease or antithrombotic agents.
2) The normal prothrombin times (INR) in the majority of subjects suggests no direct effect on vitamin K metabolism
3) The normal platelet counts while on study suggests no idiosyncratic effects on platelets. Those that developed mild thrombocytopenia, I felt, was due to underlying disease/presentation.
4) Based on the data available to me, my overall impression is that the observed AE/SAEs were most likely related to complications of the underlying diagnoses and complications of management of the underlying diseases
5) In general no particular pattern of timing of study drug to AE/SAE was obvious.
6) I am not able to comment on any possible platelet dysfunction that may have occurred as has been published in the literature with use of beta lactam antibiotics.[4] This is detectable only with complex platelet function assays which are not widely available and were not part of this study.

***M.O. comment**: Based on the cited literature on the natural history of hemorrhagic transformation of ischemic stroke and the risk of recurrence of intracranial hemorrhages, it is possible that the events of worsening intracranial hemorrhages observed in the trial could have occurred in most of these patients even without exposure to study drugs. From the 18 patients in the TOL/TAZ arm, 15 had an intracranial hemorrhage related admission diagnosis and 3 had a non-intracranial related admission diagnosis (1 cardiac arrest and 2 ischemic stroke). The mechanisms by which study drugs may have contributed to hemorrhagic transformation of ischemic stroke or worsening intracranial bleeding were assessed during the study, except for the direct inhibition of platelet function. Since TOL/TAZ does not have a methylthiotetrazole (MTT) side chain, a direct interference in the production of vitamin K dependent coagulation factors by this mechanism is not expected. The majority of subjects did not manifest thrombocytopenia or prothrombin time prolongation during the study. (b) (4) notes that one patient who had prolonged PT was diagnosed with liver failure (# (b) (6)) and had worsening intracranial hemorrhage, after being admitted for a subdural hematoma before receiving TOL/TAZ. The etiology of liver failure in this case appeared to be multifactorial, possibly by a combination of the underlying infectious disease (possible severe vitamin K deficiency or DIC), post-cardiac arrest syndrome, hypotension and concomitant study drug treatment for 8 days.*

(b) (4)

(b) (4) review of the 18 cases in TOL/TAZ and the 6 cases in meropenem arm is similar to (b) (4) report, distinguishing the 3 patients in the TOL/TAZ arm with ischemic events prior to exposure to TOL/TAZ, one of whom had a CNS hemorrhage while receiving fibrinolytic therapy. He states that one patient with brain herniation did not have evidence of CNS hemorrhage, and brain herniation was secondary to trauma. He also mentions that one of the patients had severe hepatic failure, thrombocytopenia and a prolonged prothrombin time and a had been diagnosed with subdural hematoma prior to exposure to TOL/TAZ (this patient is # (b) (6)). Of the remaining 13 patients, all of whom had intracranial bleeding, one patient

had abnormal coagulation studies, eight were no longer receiving TOL/TAZ (median 7 days, range 1-26 days) when they were experienced intracranial bleeding. He points out that 2 patients had acute renal failure, which can cause platelet dysfunction, and two had cerebral edema or uncal herniation as the cause of death.

He concluded that there was no evidence of thrombocytopenia or hypoprothrombinemia caused by TOL/TAZ, and that platelet function studies and other coagulation studies were not provided for these patients. A review of the 6 meropenem cases who experience intracranial hemorrhage did not reveal any difference in the clinical features of these patients as compared to those receiving TOL/TAZ.
His conclusion is as follows:

> *"Although thrombocytopenia and platelet dysfunction has been seen with Zosyn and immune thrombocytopenia with meropenem, there is no published evidence that TOL/TAZ impairs platelet function or causes thrombocytopenia or was responsible in this clinical trial for the progression of the intracranial pathology".*

M.O. comment: *(b) (4) concludes that there is no evidence that TOL/TAZ impairs platelet function or causes thrombocytopenia. (b) (4) also mentioned platelet dysfunction as a potential mechanism by which a drug can increase bleeding, and that platelet function studies were not available for these patients. He also identified hepatic failure in one patient as the cause of increased prothrombin time and thrombocytopenia in this patient (# (b) (6), same patient identified by (b) (4)).*

Based on the hematology consultations, FDA inquired whether Merck had conducted platelet function studies or if they were aware of any published studies that assessed platelet function with TOL/TAZ. Merck responded that no studies had been conducted to assess the impact of TOL/TAZ on platelet function. They also stated that they were not aware of any published literature on the topic. They noted that in nonclinical repeat dose studies with ceftolozane alone or with TOL/TAZ, there was no evidence of study drug related hemorrhage or microhemorrhage in the histopathological examinations performed on tissues. Merck also noted that:

> "Abnormal platelet function would be expected to increase the overall number of bleeding events throughout different anatomic sites, including sites outside the central nervous system (CNS). As noted in the responses provided to the Agency on 31-Jan-2019 and 15-Mar-2019, bleeding or hemorrhagic events outside the CNS were comparable in frequency between the treatment groups across system organ classes. In addition, the types of bleeding events typically associated with platelet dysfunction, such as bleeding from mucous membranes and at sites of minor skin trauma (i.e., intravenous line sites)(Casari and Bergmeier 2016), were very rare in PN008."

The cardiac disorders SOC followed the Nervous system disorders SOC with similar frequency of deaths in both arms. Following in frequency was the general disorders and administration conditions, also reflecting the events associated with disease progression and co-morbid conditions, with a 5.8% vs 4.2% rate in treatment and comparator arm, respectively. The most frequent PTs in this SOC were multi-organ failure, occurring in 14 patients (3.9%) in the treatment and in 9 (2.5%) in the comparator arm, respectively. The preferred terms related to infectious diseases and toxic-septic shock conditions were distributed in the Infections and infestations and the General disorders and administration site conditions, and the rates were similar between treatment arms. Please refer to Table 30 for more details.

Table 30. AEs With Fatal Outcomes by SOC and PT - Safety Population

Primary System Organ Class	Ceftolozane /Tazobactam N=105/361 (29.1%)	Meropenem N=101/359 (28.1%)
Nervous system disorders	**24 (6.6%)**	**19 (5.3%)**
Brain oedema	8 (2.2%)	8 (2.2%)
Cerebral haemorrhage	5 (1.4%)	0 (0.0%)
Brain midline shift	4 (1.1%)	1 (0.3%)
Haemorrhagic stroke	3 (0.8%)	1 (0.3%)
Haemorrhage intracranial	1 (0.3%)	0 (0.0%)
Brain injury	1 (0.3%)	1 (0.3%)
Intraventricular haemorrhage	1 (0.3%)	0
Mental impairment	1 (0.3%)	0
Neurological decompensation	1 (0.3%)	0
Apallic syndrome	0 (0.0%)	1 (0.3%)
Cerebellar haemorrhage	0 (0.0%)	1 (0.3%)
Cerebral ischaemia	0 (0.0%)	1 (0.3%)
Cerebrovascular accident	0 (0.0%)	1 (0.3%)
Ischaemic stroke	0 (0.0%)	1 (0.3%)
Spinal cord oedema	0 (0.0%)	1 (0.3%)
Wernicke's encephalopathy	0 (0.0%)	1 (0.3%)
Amyotrophic lateral sclerosis	0 (0.0%)	1 (0.3%)
Cardiac disorders	**23 (6.4%)**	**25 (7.0%)**
Cardiac failure acute	9 (2.5%)	6 (1.7%)
Cardiac failure	6 (1.7%)	3 (0.8%)
Cardiac arrest	3 (0.8%)	2 (0.6%)
Cardiovascular insufficiency	2 (0.6%)	3 (0.8%)
Acute myocardial infarction	2 (0.6%)	2 (0.6%)
Cardio-respiratory arrest	1 (0.3%)	3 (0.8%)
Acute coronary syndrome	0	1 (0.3%)
Arrhythmia	0	1 (0.3%)
Cardiogenic shock	0 (0.0%)	1 (0.3%)
Cardiopulmonary failure	0 (0.0%)	1 (0.3%)
Myocardial infarction	0 (0.0%)	1 (0.3%)
Myocardial ischaemia	0 (0.0%)	1 (0.3%)
Pulseless electrical activity	0 (0.0%)	1 (0.3%)
General disorders and administration site conditions	**21 (5.8%)**	**15 (4.2%)**
Multi-organ failure	14 (3.9%)	9 (2.5%)
Death	3 (0.8%)	4 (1.1%)
Brain death	3 (0.8%)	1 (0.3%)
Systemic inflammatory response syndrome	1 (0.3%)	0 (0.0%)
Cardiac death	0 (0.0%)	1 (0.3%)

Primary System Organ Class	Ceftolozane /Tazobactam N=105/361 (29.1%)	Meropenem N=101/359 (28.1%)
Respiratory, thoracic and mediastinal disorders	**15 (4.2%)**	**14 (3.9%)**
Respiratory failure	6 (1.7%)	4 (1.1%)
Pulmonary embolism	4 (1.1%)	4 (1.1%)
Chronic respiratory failure	1 (0.3%)	0 (0.0%)
Pneumonia aspiration	1 (0.3%)	0 (0.0%)
Acute pulmonary oedema	1 (0.3%)	0 (0.0%)
Acute respiratory failure	1 (0.3%)	2 (0.6%)
Acute respiratory distress syndrome	1 (0.3%)	1 (0.3%)
Respiratory arrest	0 (0.0%)	1 (0.3%)
Respiratory distress	0 (0.0%)	1 (0.3%)
Chronic obstructive pulmonary disease	0 (0.0%)	1 (0.3%)
Infections and infestations	**14 (3.9%)**	**20 (5.6%)**
Septic shock	8 (2.2%)	9 (2.5%)
Sepsis	3 (0.8%)	2 (0.6%)
Pneumonia	2 (0.6%)	2 (0.6%)
Lung abscess	1 (0.3%)	0 (0.0%)
Bronchopneumonia	0 (0.0%)	1 (0.3%)
Device related sepsis	0 (0.0%)	1 (0.3%)
Encephalitis	0 (0.0%)	1 (0.3%)
Endotoxemia	0 (0.0%)	1 (0.3%)
Gangrene	0 (0.0%)	1 (0.3%)
Peritonitis	0 (0.0%)	1 (0.3%)
Pneumonia bacterial	0 (0.0%)	1 (0.3%)
Injury, poisoning and procedural complications	**3 (0.8%)**	**1 (0.3%)**
Brain herniation	3 (0.8%)	1 (0.3%)
Vascular disorders	**3 (0.8%)**	**3 (0.8%)**
Hypovolaemic shock	2 (0.6%)	2 (0.6%)
Neurogenic shock	1 (0.3%)	0 (0.0%)
Shock haemorrhagic	0 (0.0%)	1 (0.3%)
Gastrointestinal disorders	**2 (0.6%)**	**4 (1.1%)**
Upper gastrointestinal haemorrhage	1 (0.3%)	1 (0.3%)
Gastrointestinal ischaemia	1 (0.3%)	0 (0.0%)
Gastrointestinal necrosis	0 (0.0%)	1 (0.3%)
Gastrointestinal haemorrhage	0 (0.0%)	2 (0.6%)
Metabolism and nutrition disorders	**1 (0.3%)**	**1 (0.3%)**
Metabolic acidosis	1 (0.3%)	0 (0.0%)
Failure to thrive	0 (0.0%)	1 (0.3%)
Renal and urinary disorders	**0 (0.0%)**	**1 (0.3%)**
Renal failure acute	0 (0.0%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0 (0.0%)**	**1 (0.3%)**
Malignant peritoneal neoplasm	0 (0.0%)	1 (0.3%)

Table 31. Distribution of Deaths by Selected Baseline Characteristics

	Ceftolozane N=106		Meropenem N=101	
Baseline Characteristic	Patients who died	Total N in the study	Patients who died	Total N in the study
Region				
Non-U.S.	101 (29.2)	346	98 (28.5)	344
U.S.	4 (26.7)	15	3 (20.0)	15

Baseline Characteristic	Ceftolozane N=106		Meropenem N=101	
	Patients who died	Total N in the study	Patients who died	Total N in the study
Primary diagnosis (STRAT1)				
VABP	74 (28.2)	262	60 (23.6)	254
Ventilated HABP	31 (31.3)	99	41 (39.0)	105
Age stratification (STRAT2)				
<65	43 (21.4)	201	40 (19.8)	202
≥65	62 (38.8)	160	61 (38.9)	157
Baseline creatinine clearance				
>50 - <80 mL/min (mild impairment)	34 (41.4)	82	27 (35.1)	77
≥15 - <30 mL/min (severe impairment)	8 (47.1)	17	13 (61.9)	21
≥150 mL/min (hyperclearance)	13 (19.4)	67	8 (12.5)	64
≥30 - ≤50 mL/min (moderate impairment)	13 (37.1)	35	11 (42.3)	26
≥80 - <150 mL/min (normal)	38 (23.8)	160	42 (24.6)	171
Baseline APACHE score				
<20	57 (24.1)	237	61 (24.9)	245
≥20	49 (39.5)	124	40 (35.4)	113
Age group				
<75 Years	67 (24.3)	276	70 (24.7)	283
≥75 Years	39 (47.6)	82	31 (41.9)	74

Source: ADSL, ADAE, AESDTH flag, safety population

8.2.4.2. Serious Adverse Events

The incidence of serious adverse events was approximately 6% higher in the TOL/TAZ group (42.1%) compared to the meropenem group (35.9%). As expected, in both treatment arms, relatively higher percentages of SAEs were observed in patients age 65 and older and were highest in those aged 75 and above [46/83 (55%) and 35/75 (46%) in TOL/TAZ and meropenem recipients aged 75 and above, respectively]. The small sample size of the oldest age group is a limitation to comparing rates with those of the other age groups. However, in all age groups, SAE rates were consistently higher in the TOL/TAZ arm than in the meropenem arm by at least 5%. The rate difference was greater in the older age groups, higher in TOL/TAZ by 7% in the 65-year-olds and older and by 9% in the 75-year-olds and older. In the group of patients with baseline APACHE II scores of 20 and above, the rates were higher in both treatment arms, with approximately 9% higher rate in the TOL/TAZ arm relative to the meropenem arm (63/124 or 50.8% and 47/113 or 41.5%, in TOL/TAZ and meropenem arms, respectively). Similar trends and differences were observed in SAE rates by baseline creatinine clearance, however, the size of these subgroups is too small to make any conclusions. Higher rates in the TOL/TAZ arm were observed in the hyperclearance (>150 mL/min) group, where 20/67 (29.8%) and, 15/64 (23.4%) were observed in TOL/TAZ and meropenem groups, respectively. When considering the group of mild, moderate and severe together, the rates were 74/134 (55%) in TOL/TAZ and 58/124 (46.7%) in meropenem groups. In the group with normal baseline creatinine clearance, 59/160 (36.8%) had SAEs in the TOL/TAZ arm, and 56/171 (32.7%) in the meropenem arm. The trend of higher rates of SAEs in the TOL/TAZ arm is consistent with that observed in the whole study population. There were no substantial differences or definite trends in the SAE rates among the treatment arms when stratified by the 5 baseline creatinine clearance categories, shown in

Table 32 below. The sizes of these 5 subgroups are small and variable in size, with comparable distribution by treatment arm. Comparison among these subgroups per treatment arm has limitations, given the small sizes of the subgroups of lower creatinine clearances as compared to the group who had normal creatinine clearance at baseline, which was much larger.

Table 32. SAE Rates by Baseline Creatinine Clearance Categories - Safety Population

	SAE Rates by Baseline CrCl	
Baseline Creatinine Clearance Category	**TOL/TAZ**	**Meropenem**
>50 - <80 mL/min (mild impairment)	43/82 (52.4%)	30/77 (38.9%)
≥15 - <30 mL/min (severe impairment)	10/17 (58.8%)	15/21 (71.4%)
≥150 mL/min (hyperclearance)	20/67 (29.8%)	15/64 (23.4%)
≥30 - ≤50 mL/min (moderate impairment)	21/35 (60%)	13/26 (50%)
≥80 - <150 mL/min (normal)	59/160 (36.8%)	56/171 (32.7%)

In the overall study population, septic shock and multi-organ failure, representing progression of the underlying disease, were the most commonly reported SAEs with similar rates in both treatment arms. Acute renal failure was the SAE with the highest risk difference in the treatment arm, reported in 9/361 (2.49%) TOL/TAZ patients and in 3/351 (0.84%) of meropenem recipients. *C. difficile* colitis and related terms (reported as SAEs) were observed at a higher frequency in the treatment arm (3/361 or 0.83% and 1/351 or 0.28%). The Applicant performed a post-hoc analysis to compare rates of SAEs in each arm, with corresponding 95% CI of the rate ratio. Of the hemorrhages at other body sites, SAEs of gastrointestinal hemorrhage terms were the most frequent events, reported at similar rates in the treatment arm relative to the comparator arm (the SMQ “gastrointestinal hemorrhage” for MedDRA version 17, showed an incidence of 2.77% and 1.95%, in treatment and comparator arms, respectively). SAEs related to liver disorders, shock and cardiac conditions were similar in frequency in both treatment arms, reported at a relatively low incidence. Table 33 below shows all Serious Adverse Events reported by MedDRA SOC and PT.

Table 33. Serious Adverse Events by SOC and PT - Safety Population

Primary System Organ Class	Ceftolozane/ Tazobactam N=152/361 (42.1%)	Meropenem N=129/359 (35.9%)
Cardiac disorders	35 (9.7%)	37 (10.3%)
Cardiac failure acute	9 (2.5%)	7 (1.9%)
Cardiac arrest	8 (2.2%)	6 (1.7%)
Cardiac failure	7 (1.9%)	3 (0.8%)
Cardio-respiratory arrest	4 (1.1%)	4 (1.1%)
Acute myocardial infarction	2 (0.6%)	2 (0.6%)
Ventricular fibrillation	2 (0.6%)	0 (0.0%)
Cardiovascular insufficiency	2 (0.6%)	4 (1.1%)
Ventricular tachycardia	1 (0.3%)	2 (0.6%)
Bradycardia	1 (0.3%)	1 (0.3%)
Acute coronary syndrome	0	1 (0.3%)
Arrhythmia	0 (0.0%)	1 (0.3%)
Cardiac failure chronic	0 (0.0%)	1 (0.3%)
Cardiogenic shock	0 (0.0%)	1 (0.3%)
Cardiopulmonary failure	0 (0.0%)	1 (0.3%)
Coronary artery occlusion	0 (0.0%)	1 (0.3%)
Myocardial infarction	0 (0.0%)	1 (0.3%)
Myocardial ischaemia	0 (0.0%)	1 (0.3%)
Pulseless electrical activity	0 (0.0%)	1 (0.3%)
Supraventricular tachycardia	0 (0.0%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	34 (9.4%)	27 (7.5%)
Respiratory failure	10 (2.8%)	6 (1.7%)
Pulmonary embolism	6 (1.7%)	5 (1.4%)
Pneumothorax	4 (1.1%)	0 (0.0%)
Acquired tracheo-oesophageal fistula	3 (0.8%)	0 (0.0%)
Pneumonia aspiration	3 (0.8%)	0 (0.0%)
Acute respiratory distress syndrome	2 (0.6%)	2 (0.6%)
Mediastinal effusion	1 (0.3%)	0 (0.0%)
Pneumomediastinum	1 (0.3%)	0 (0.0%)
Chronic respiratory failure	1 (0.3%)	0 (0.0%)
Acute respiratory failure	1 (0.3%)	5 (1.4%)
Lung disorder	1 (0.3%)	0 (0.0%)
Dyspnoea	1 (0.3%)	0 (0.0%)
Respiratory distress	1 (0.3%)	1 (0.3%)
Acute pulmonary oedema	1 (0.3%)	0 (0.0%)
Tracheal stenosis	1 (0.3%)	0 (0.0%)
Aspiration	0 (0.0%)	1 (0.3%)
Atelectasis	0 (0.0%)	1 (0.3%)
Chronic obstructive pulmonary disease	0 (0.0%)	2 (0.6%)
Organising pneumonia	0 (0.0%)	1 (0.3%)
Pleural effusion	0 (0.0%)	1 (0.3%)
Respiratory arrest	0 (0.0%)	1 (0.3%)
Acute lung injury	0 (0.0%)	1 (0.3%)

Primary System Organ Class	Ceftolozane/ Tazobactam N=152/361 (42.1%)	Meropenem N=129/359 (35.9%)
Infections and infestations	31 (8.6%)	34 (9.5%)
Septic shock	13 (3.6%)	14 (3.9%)
Sepsis	5 (1.4%)	3 (0.8%)
Clostridium difficile colitis	3 (0.8%)	0 (0.0%)
Pneumonia	3 (0.8%)	3 (0.8%)
Abdominal infection	1 (0.3%)	0 (0.0%)
Klebsiella sepsis	1 (0.3%)	0 (0.0%)
Lung abscess	1 (0.3%)	0 (0.0%)
Bacteraemia	1 (0.3%)	0 (0.0%)
Enterobacter bacteraemia	1 (0.3%)	0 (0.0%)
Abscess neck	1 (0.3%)	0 (0.0%)
Septic encephalopathy	1 (0.3%)	0 (0.0%)
Abdominal abscess	1 (0.3%)	0 (0.0%)
Urinary tract infection	1 (0.3%)	0 (0.0%)
Urosepsis	1 (0.3%)	0 (0.0%)
Bronchopneumonia	0 (0.0%)	1 (0.3%)
CNS ventriculitis	0 (0.0%)	1 (0.3%)
Clostridium difficile infection	0 (0.0%)	1 (0.3%)
Device related sepsis	0 (0.0%)	1 (0.3%)
Encephalitis	0 (0.0%)	1 (0.3%)
Endocarditis	0 (0.0%)	1 (0.3%)
Endocarditis bacterial	0 (0.0%)	1 (0.3%)
Endotoxaemia	0 (0.0%)	1 (0.3%)
Gangrene	0 (0.0%)	1 (0.3%)
Meningitis	0 (0.0%)	3 (0.8%)
Peritonitis	0 (0.0%)	3 (0.8%)
Pneumonia bacterial	0 (0.0%)	1 (0.3%)
Nervous system disorders	28 (7.8%)	23 (6.4%)
Brain oedema	8 (2.2%)	8 (2.2%)
Cerebral haemorrhage	5 (1.4%)	0 (0.0%)
Brain midline shift	4 (1.1%)	1 (0.3%)
Haemorrhagic stroke	3 (0.8%)	1 (0.3%)
Cerebral haematoma	1 (0.3%)	0 (0.0%)
Cerebral vasoconstriction	1 (0.3%)	0 (0.0%)
Cerebrovascular accident	1 (0.3%)	1 (0.3%)
Cognitive disorder	1 (0.3%)	0 (0.0%)
Haemorrhage intracranial	1 (0.3%)	0 (0.0%)
Brain injury	1 (0.3%)	1 (0.3%)
Intracranial pressure increased	1 (0.3%)	0 (0.0%)
Intraventricular haemorrhage	1 (0.3%)	0 (0.0%)
Ischaemic cerebral infarction	1 (0.3%)	0 (0.0%)
Neurological decompensation	1 (0.3%)	0 (0.0%)
Amyotrophic lateral sclerosis	0 (0.0%)	1 (0.3%)
Apallic syndrome	0 (0.0%)	1 (0.3%)
Cerebellar haemorrhage	0 (0.0%)	1 (0.3%)
Cerebral infarction	0 (0.0%)	1 (0.3%)
Cerebral ischaemia	0 (0.0%)	2 (0.6%)
Dementia Alzheimer's type	0 (0.0%)	1 (0.3%)
Hydrocephalus	0 (0.0%)	2 (0.6%)
Ischaemic stroke	0 (0.0%)	1 (0.3%)
Parkinson's disease	0 (0.0%)	1 (0.3%)

Primary System Organ Class	Ceftolozane/ Tazobactam N=152/361 (42.1%)	Meropenem N=129/359 (35.9%)
Spinal cord oedema	0 (0.0%)	1 (0.3%)
Wernicke's encephalopathy	0 (0.0%)	1 (0.3%)
General disorders and administration site conditions	21 (5.8%)	16 (4.5%)
Multi-organ failure	14 (3.9%)	9 (2.5%)
Death	3 (0.8%)	4 (1.1%)
Brain death	3 (0.8%)	1 (0.3%)
Systemic inflammatory response syndrome	1 (0.3%)	0 (0.0%)
Pyrexia	0 (0.0%)	1 (0.3%)
Cardiac death	0 (0.0%)	1 (0.3%)
Gastrointestinal disorders	17 (4.7%)	9 (2.5%)
Gastrointestinal haemorrhage	4 (1.1%)	3 (0.8%)
Gastritis erosive	1 (0.3%)	0 (0.0%)
Gastroduodenal haemorrhage	1 (0.3%)	0 (0.0%)
Gastric haemorrhage	1 (0.3%)	0 (0.0%)
Abdominal pain	1 (0.3%)	0 (0.0%)
Gastrointestinal ischaemia	1 (0.3%)	0 (0.0%)
Haematemesis	1 (0.3%)	1 (0.3%)
Haemorrhagic erosive gastritis	1 (0.3%)	0 (0.0%)
Hernial eventration	1 (0.3%)	0 (0.0%)
Ileus	1 (0.3%)	0 (0.0%)
Ileus paralytic	1 (0.3%)	0 (0.0%)
Intestinal ischaemia	1 (0.3%)	0 (0.0%)
Pneumoperitoneum	1 (0.3%)	0 (0.0%)
Small intestinal obstruction	1 (0.3%)	0 (0.0%)
Upper gastrointestinal haemorrhage	1 (0.3%)	2 (0.6%)
Gastrointestinal necrosis	0 (0.0%)	1 (0.3%)
Peptic ulcer	0 (0.0%)	1 (0.3%)
Duodenal ulcer haemorrhage	0 (0.0%)	1 (0.3%)
Renal and urinary disorders	12 (3.3%)	4 (1.1%)
Renal failure acute	9 (2.5%)	3 (0.8%)
Renal failure	2 (0.6%)	1 (0.3%)
Hydronephrosis	1 (0.3%)	0 (0.0%)
Injury, poisoning and procedural complications	10 (2.8%)	4 (1.1%)
Brain herniation	3 (0.8%)	2 (0.6%)
Bladder injury	1 (0.3%)	0 (0.0%)
Abdominal wound dehiscence	1 (0.3%)	0 (0.0%)
Endotracheal intubation complication	1 (0.3%)	0 (0.0%)
Gastrointestinal anastomotic leak	1 (0.3%)	0 (0.0%)
Gastrointestinal stoma complication	1 (0.3%)	0 (0.0%)
Post procedural haemorrhage	1 (0.3%)	0 (0.0%)
Splenic injury	1 (0.3%)	0 (0.0%)
Tracheal haemorrhage	1 (0.3%)	0 (0.0%)
Tracheal injury	1 (0.3%)	0 (0.0%)
Subdural haematoma	0 (0.0%)	1 (0.3%)
Procedural haemorrhage	0 (0.0%)	1 (0.3%)

Primary System Organ Class	Ceftolozane/ Tazobactam N=152/361 (42.1%)	Meropenem N=129/359 (35.9%)
Vascular disorders	5 (1.4%)	4 (1.1%)
Hypovolaemic shock	2 (0.6%)	2 (0.6%)
Haemodynamic instability	1 (0.3%)	0 (0.0%)
Neurogenic shock	1 (0.3%)	0 (0.0%)
Peripheral ischaemia	1 (0.3%)	0 (0.0%)
Arterial thrombosis	1 (0.3%)	0 (0.0%)
Shock haemorrhagic	0 (0.0%)	1 (0.3%)
Hypotension	0 (0.0%)	1 (0.3%)
Metabolism and nutrition disorders	2 (0.6%)	4 (1.1%)
Metabolic acidosis	2 (0.6%)	0 (0.0%)
Failure to thrive	0 (0.0%)	1 (0.3%)
Hyperkalaemia	0 (0.0%)	1 (0.3%)
Dehydration	0 (0.0%)	2 (0.6%)
Ear and labyrinth disorders	1 (0.3%)	0 (0.0%)
Deafness neurosensory	1 (0.3%)	0 (0.0%)
Congenital, familial and genetic disorders	1 (0.3%)	0 (0.0%)
Cerebral arteriovenous malformation haemorrhagic	1 (0.3%)	0 (0.0%)
Hepatobiliary disorders	1 (0.3%)	1 (0.3%)
Investigations	1 (0.3%)	1 (0.3%)
Aspartate aminotransferase increased	1 (0.3%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.3%)	0 (0.0%)
Alanine aminotransferase increased	1 (0.3%)	0 (0.0%)
Creatinine renal clearance decreased	0 (0.0%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	2 (0.6%)
Renal cancer	0 (0.0%)	1 (0.3%)
Malignant peritoneal neoplasm	0 (0.0%)	1 (0.3%)
Blood and lymphatic system disorders	0 (0.0%)	2 (0.6%)
Thrombocytopenia	0 (0.0%)	1 (0.3%)
Anaemia	0 (0.0%)	1 (0.3%)

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of TEAEs leading to discontinuation of study drug (39/361 or 9.97% for ceftolozane/tazobactam versus 42/359 or 11.7% for meropenem) were comparable between the treatment groups. The most common reason for premature withdrawal from the study or discontinuation of study drug were SAEs (32 of the 38 patients in the treatment arm and 35 of the 42 patients in the comparator arm had SAEs leading to study drug being withdrawn), and the majority of these SAEs resulted in death (22 and 31 of patients with AEs leading to study drug discontinuation had fatal AE outcomes in the treatment and comparator arms, respectively). The most common AE by preferred term in the treatment arm was renal failure acute, which only occurred in the treatment arm (5 or 1.4% and 0 in the treatment arm), which was also the preferred term with highest risk difference. The renal and urinary disorders SOC also showed the highest risk difference, with 6 vs 1 patients in the treatment and comparator arms, respectively.

Nervous system disorders was the SOC with highest incidence of events in both arms, 1.99% in the treatment arm and 2.51% in the comparator arm. These represented cerebrovascular events (brain edema, midline shift, cerebral ischemia and hemorrhagic stroke).

Most of the other PTs were observed at a similar rate among treatment arms and represented events related to progression of disease and underlying co-morbidities (septic shock, cardiac failure, multiorgan failure, pulmonary embolism). Table 34 below shows all AEs leading to discontinuation by preferred term and treatment arm.

Table 34. Adverse Events Leading to Discontinuation by Preferred Term - Safety Population

Dictionary Derived Term	Ceftolozane/Tazobactam N=38/361 (10.5%)	Meropenem N=42/359 (11.7%)
Renal failure acute	5 (1.4%)	0 (0.0%)
Septic shock	4 (1.1%)	5 (1.4%)
Brain oedema	4 (1.1%)	4 (1.1%)
Cardiac failure acute	2 (0.6%)	2 (0.6%)
Brain herniation	2 (0.6%)	1 (0.3%)
Brain midline shift	2 (0.6%)	1 (0.3%)
Multi-organ failure	2 (0.6%)	1 (0.3%)
Bronchial obstruction	1 (0.3%)	0 (0.0%)
Cardiac arrest	1 (0.3%)	1 (0.3%)
Alanine aminotransferase increased	1 (0.3%)	0 (0.0%)
Brain death	1 (0.3%)	0 (0.0%)
Cardio-respiratory arrest	1 (0.3%)	0 (0.0%)
Abscess neck	1 (0.3%)	0 (0.0%)
Haemorrhagic stroke	1 (0.3%)	1 (0.3%)
Hepatic enzyme increased	1 (0.3%)	3 (0.8%)
Hepatic failure	1 (0.3%)	0 (0.0%)
Hepatitis cholestatic	1 (0.3%)	1 (0.3%)
Interstitial lung disease	1 (0.3%)	0 (0.0%)
Klebsiella sepsis	1 (0.3%)	0 (0.0%)
Metabolic acidosis	1 (0.3%)	0 (0.0%)
Aspartate aminotransferase increased	1 (0.3%)	0 (0.0%)
Pulmonary embolism	1 (0.3%)	1 (0.3%)
Renal failure	1 (0.3%)	0 (0.0%)
Mental impairment	1 (0.3%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.3%)	0 (0.0%)
Small intestinal obstruction	1 (0.3%)	0 (0.0%)
Transaminases increased	1 (0.3%)	0 (0.0%)
Acute coronary syndrome	0 (0.0%)	1 (0.3%)
Acute myocardial infarction	0 (0.0%)	2 (0.6%)
Apallic syndrome	0 (0.0%)	1 (0.3%)
Bronchopneumonia	0 (0.0%)	1 (0.3%)
CNS ventriculitis	0 (0.0%)	1 (0.3%)
Cardiopulmonary failure	0 (0.0%)	1 (0.3%)
Cerebral ischaemia	0 (0.0%)	1 (0.3%)
Encephalitis	0 (0.0%)	1 (0.3%)
Eosinophilia	0 (0.0%)	1 (0.3%)
Gastrointestinal haemorrhage	0 (0.0%)	1 (0.3%)
Malignant peritoneal neoplasm	0 (0.0%)	1 (0.3%)

Dictionary Derived Term	Ceftolozane/Tazobactam N=38/361 (10.5%)	Meropenem N=42/359 (11.7%)
Meningitis	0 (0.0%)	1 (0.3%)
Meningitis bacterial	0 (0.0%)	1 (0.3%)
Myocardial ischaemia	0 (0.0%)	1 (0.3%)
Pancytopenia	0 (0.0%)	1 (0.3%)
Rash	0 (0.0%)	1 (0.3%)
Renal impairment	0 (0.0%)	1 (0.3%)
Respiratory failure	0 (0.0%)	3 (0.8%)
Spinal cord oedema	0 (0.0%)	1 (0.3%)
Subjects(filtered)		

Source: ADSL, ADAE*SAS*,Safety population, Action Taken with Study Treatment =DRUG WITHDRAWN "Y"] Applicant's derived flags.

8.2.4.4. Significant Adverse Events

Based on the known safety profile of ceftolozane/tazobactam and/or potential drug class effects, the following adverse events were summarized by the Applicant:

- Severe skin reaction/hypersensitivity
- *Clostridium difficile*-associated diarrhea
- Renal dysfunction
- Emergence of bacterial resistance

In addition, the following laboratory results were summarized:

- Direct Coombs' test conversion (shifts from negative baseline result to a positive result at EOT)
- Laboratory criteria for potential Drug-Induced Liver Injury, including patients who met the laboratory criteria for Hy's Law
- Renal dysfunction events

Hypersensitivity

There were no severe hypersensitivity reactions (e.g., anaphylaxis) and no severe cutaneous TEAEs suggestive of a severe cutaneous adverse reaction among subjects exposed to TOL/TAZ in PN008. A review of the SMQ "Hypersensitivity", which included the following terms: *urticaria, laryngeal edema, catheter site urticaria, allergic transfusion reaction, dermatitis, dermatitis contact, dermatitis allergic, bronchospasm, rash, rash erythematous, toxic skin eruption, eczema, skin necrosis, rhinitis allergic, scrotal edema, face edema, rash pustular, drug hypersensitivity*, revealed a total of 19/361 (5.3%) cases in the TOL/TAZ arm and 25/351 (7.0%) in the meropenem arm.

***Clostridium difficile*-associated diarrhea**

The overall incidence of events related to *C. difficile* was relatively low, however, it was more than two-fold higher in the TOL/TAZ arm than in the meropenem arm. The SMQ

"Pseudomembranous colitis" revealed cases reported with the following PTs: *Clostridium difficile* colitis*, Clostridium difficile* infection and *Clostridium* test positive. An individual review of the CRFs further confirmed the presence of associated diarrhea in all these patients. There were 10 (2.8%) cases of *C. difficile* colitis/pseudomembranous colitis and 2 (0.6%) in the meropenem arm. In the treatment arm, 3 of the 10 cases were serious adverse events and in the comparator arm, 1 of 2 were serious adverse events. All events resolved except for one in which the patient died (subject (b) (6), TOL/TAZ arm) due to an intracranial hemorrhage while he was being treated for *C. difficile* associated diarrhea.

Direct Coombs' test conversion (shifts from negative baseline result to a positive result at EOT)

Rates of seroconversion from a negative Coombs' test at baseline to a positive at EOT occurred in a higher proportion of patients in the TOL/TAZ group compared with meropenem in PN008. A total of 93 (30.2%) patients in the TOL/TAZ arm and 11 (3.5%) in the meropenem arm had shifts from a direct Coombs' test negative to a positive result at EOT. Anemia as a PT was reported in 13/93 (14%) patients, however, no specific work-up for hemolytic anemia was performed (no LDH, haptoglobin or reticulocytes measurements were reported in this submission). The presence of other potential causes for anemia in these patients precludes any conclusion about the clinical significance of the Direct Coombs test conversion. However, a review of reported terms related to anemia in the study revealed that there were no increased rates of anemia in the treatment arm as compared with the meropenem arm overall. In fact, anemia was reported at slightly higher rates in the meropenem arm. Higher direct Coombs' conversion rates were also observed following the 3 g dose of TOL/TAZ in PN008 compared with those in the Phase 1 and Phase 3 studies using the 1.5 g dose of TOL/TAZ, however, it was similar to the incidence reported in patients treated with another cephalosporin for treatment of HABP/VABP.

Laboratory criteria for potential Drug-Induced Liver Injury, including patients who met the laboratory criteria for Hy's Law

Overall, 6 subjects met the laboratory criteria for potential Drug-Induced Liver Injury in PN008, 2 in the TOL/TAZ arm and 4 in the meropenem arm. The 2 subjects in the TOL/TAZ group had medical histories of liver disease prior to study enrollment, 1 of whom met the laboratory criteria for potential Drug-Induced Liver Injury at baseline. The 4 subjects in the meropenem group were critically ill with confounding concurrent medical conditions. A description of these cases is provided below.

Patients with Laboratory Criteria for Hy's Law

TOL/TAZ Arm:

Subject ID (b) (6) – Country: Czech Republic

Subject (b) (6) was a 66-year-old white female who had a medical history of hepatic steatosis (diagnosed pre-study on June 9, 2005 based on the findings of a liver ultrasound). The subject was admitted to the hospital on (b) (6) with acute respiratory failure. The same day, she experienced a cardiac arrest and was intubated. On admission the subject was diagnosed with ventilated hospital acquired bacterial pneumonia (vHABP), related to her discharge from a prior hospitalization 5 days earlier for bimalleolar ankle fracture, which was treated conservatively without surgery. The subject was enrolled in the study on the day of admission and in addition to study therapy was initiated on protocol-mandated adjunctive treatment with linezolid and protocol-allowed adjunctive Gram-negative therapy with amikacin. At baseline and prior to the first dose of study medication, the subject's aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin were elevated (see Table 35 below). At the time of entry into the study the subject was being treated for liver steatosis with Essentiale Forte (polyene phosphatidylcholine). An abdominal ultrasound on Study Day 1 showed diffuse liver steatosis, with no focal changes in the liver parenchyma and no free fluid in the peritoneal cavity. On Study Day 4 the subject was recorded as having a non-serious adverse event of abnormal liver function tests which met laboratory criteria for Hy's law and which the investigator assessed as moderate in intensity and not related to the study therapy. Study therapy was continued unchanged, for a total duration of 10 days. The investigator reported that the rise in liver function tests was most likely due to liver hypoperfusion and hypoxia due to the cardiac arrest the patient experienced on Study Day 1. The Applicant's assessment concurs.
On Day (b) (6), an SAE of brain death was confirmed by a neurologist and palliative therapy was started. However, the subject died on the same day due to brain death.

Table 35. Relevant Laboratory Tests Results

Study Day	ALT, U/L NR: 0-33	AST, U/L NR: 14-34	ALP, U/L NR: 42-98	Total Bilirubin, µmol/L NR: 5.1-20.5
Screening/baseline	57	37	108	44.2
Day 4	116	166	94	75.4
Day 9	284	396	162	89.1
Day 10 (EOT)	302	384	175	124.1

NR: normal range; EOT: end of treatment visit – Source: PN008 CSR, Section 16.2.7.2

M.O. comment: *This subject's diagnosis of pre-existing liver steatosis and subsequent post-cardiac arrest hypoperfusion and hypoxia can explain the hepatotoxicity observed during treatment with TOL/TAZ. Because of the temporal relationship of this liver related AE to treatment and the known association of TOL/TAZ with increase in transaminases in clinical*

studies, it is not possible to exclude a potential drug contribution to the liver toxicity observed in this case.

Subject ID (b) (6) – Country: Serbia

Patient (b) (6) was a 65-year-old white male. He had a diagnosis of cirrhosis in his medical history. On Day 1, the subject was diagnosed with VABP and study medication was initiated. In addition, protocol-mandated Gram-positive adjunctive therapy with linezolid was initiated (stopped on Day 3). The last dose of the study medication was given on Day 9. At the EOT visit on the same day, the clinical response was "cure."
LFT results met the laboratory criteria for Hy's Law (ALT or AST >3 × ULN, ALP ≤2.0 × ULN, and total bilirubin >2.0 × ULN) at baseline (prior to the subject receiving study medication) and at all time points through Day 9, which was the last day of treatment (total duration of treatment was 9 days). On Day 11, the subject experienced an upper GI hemorrhage and was treated with pantoprazole and sodium chloride. Despite treatment, on Day (b) (6) the subject's condition worsened; the subject was disoriented and hypotensive. On the same day, the subject had massive melena and developed an SAE of severe hypovolemic shock due to bleeding from a stomach ulcer and had a cardiac arrest. CPR was performed, and epinephrine and sodium bicarbonate were administered, but the subject died due to hypovolemic shock.

Table 36. Laboratory Findings for Subject (b) (6)

Study Day	ALT, U/L NR: 0-44	AST, U/L NR: 14-39	ALP, U/L NR: 53-129	Total Bilirubin, µmol/L NR: 5.1-20.5
Screening/baseline	80	209	142	60.4
Day 3	78	154	123	92.8
Day 8	87	129	135	182.6
Day 9 (EOT)	90	131	166	193.5

NR: normal range; EOT: end of treatment visit – Source: PN008 CSR, section 16.2.7.2

M.O. comment: *This patient had chronic liver disease, cirrhosis, and an ongoing serious infection. He suffered complications from hypovolemia after gastrointestinal bleeding. Platelet values were not provided. His chronic liver disease, the ongoing infection and massive bleeding are likely causes of his hepatotoxicity. The potential contribution of the study drug to his developing hepatotoxicity cannot be ruled out because of the temporal association and the known association of TOL/TAZ with increased liver enzymes during treatment.*

In addition to these two cases, there were two other cases reported as "liver failure", although they did not meet laboratory criteria for Hy's law. Both patients were severely ill and died from adverse events related to complications of their underlying conditions. The events of hepatic failure were ongoing at the time of death and had an outcome of "not recovered/not resolved".

These were patients (b) (6), a 50-year-old white female from Georgia and (b) (6), an 84-year-old white male from Belgium. Both these patients died, a summary is presented below.

Subject ID (b) (6)

Patient (b) (6), a 50-year-old white female, was diagnosed with VABP. Relevant medical history included multiple injuries, coma, quadriparesis, and "hypocoagulable state". She had been admitted on Day (b) (6) after cardiac arrest. On admission, she was also diagnosed with anemia, acute liver failure, respiratory failure, hypotension, and cardiovascular insufficiency. On Day -3 the subject experienced a subdural hematoma. On Day 6, the patient had a hemorrhagic stroke and was diagnosed with a cerebral hematoma (severe) and brain edema. On the same day, evacuation of hematoma was performed, and the SAE of cerebral hematoma was considered resolved. The baseline acute hepatic failure worsened based on rising transaminases, bilirubin increase of 1.5 times the ULN, and thrombocytopenia and a drug-related non-serious AE of hepatic failure (severe) was reported. Study medication was permanently discontinued due to the event of hepatic failure on Day 6. The investigator considered the event of hepatic failure as related to study drug. Adverse events of cerebral hemorrhage and brain edema were reported also on Day 6. The last dose of study medication was given on Day 7, and the patient died on Day (b) (6). A table with the liver tests results is presented below.

Table 37. Laboratory Findings for Subject (b) (6)

Study Day	ALT, U/L NR: 0-33	AST, U/L NR: 14-34	ALP, U/L NR: 42-98	Total Bilirubin, µmol/L NR: 5.1-20.5
Screening/baseline	73	20	146	15.1
Day 3	32	20	172	26
Day 8	20	19	86	31.5

M.O. comment: *This patient had a subdural hematoma on admission 6 days prior to starting study drug, and bleeding around her tracheostomy was noted before exposure to study drug. The laboratory data submitted are not complete to be able to confirm possible baseline hepatotoxicity on admission, which could be a potential cause for increased risk of bleeding in this case. This patient had a severe infection, with possible vitamin K deficiency, or DIC. Because of the temporal association with study drug and the event of hepatic failure, increased prothrombin time and thrombocytopenia, and the known association of increased transaminases with TOL/TAZ treatment, a potential contribution of study drug to the worsening of hepatic function cannot be ruled out.*

Subject ID (b) (6)

Patient (b) (6), an 84-year-old white male, with medical history relevant for diabetes, was diagnosed with VABP and treated with TOL/TAZ for a total of (b) (6) days, after being admitted with acute myocardial infarction, cardiac arrest, cardiogenic shock, and oliguria. Also prior to enrollment into the study, the patient reportedly experienced septic shock, hyperkalemia,

hyponatremia, fluid imbalance, pulmonary edema, bronchospasm, and ARDS. His creatinine clearance on screening was 55.6 mL/min. On Day 3, the laboratory results showed creatinine of 2.14 mg/dL (baseline: 1.1 mg/dL), ALT of 149 U/L (baseline: 42 U/L; NR: 0-44 U/L), AST of 277 U/L (baseline: 76 U/L; NR: 14-39 U/L), ALP of 287 U/L (baseline: 70 U/L; NR: 53-129 U/L), and bilirubin of 3.8 µmol/L (baseline: 5.7 µmol/L; NR: 5.1-20.5 µmol/L) and was diagnosed with an SAE of acute renal failure and a non-serious AE of hepatic failure. His TOL/TAZ dose was reduced to 750 mg/day on day 3. He had an AE of hyperkalemia on day 4. On day 5, his creatinine clearance was 14 mL/min. On Day 6, study medication was permanently discontinued due to the event of acute renal failure. On Day 7 he experienced ARDS and he died on Day (b) (6) from refractory ARDS. A table with liver test results is shown below.

Table 38. Laboratory Findings for Subject (b) (6)

Study Day	ALT, U/L NR: 0-44	AST, U/L NR: 14-39	ALP, U/L NR: 53-129	Total Bilirubin, µmol/L NR: 5.1-20.5
Screening/baseline	42	76	70	5.7
Day 3	149	277	287	3.8

M.O. comment: *In this elderly patient with diabetes and severe pneumonia, the event of hepatic failure was observed in temporal association with study drug. The present significant co-morbidities of diabetes, severe infection, including septic shock, and renal failure are probable causative factors to the hepatotoxicity observed. A contribution of the study drug to this event cannot be ruled out because of the temporal relationship to treatment and the known association with increases in transaminases of TOL/TAZ during treatment. The possibility of a relatively higher exposure to TOL/TAZ due to rapidly decreased creatinine clearance cannot be ruled out, even though the TOL/TAZ dose was adjusted on Day 3. The investigator did not consider the events as related to study drug.*

In addition to these cases, there was one non-fatal SAE of cholestatic hepatitis in the TOL/TAZ arm (and one in the meropenem arm, discussed later). Another non-fatal SAE in the TOL/TAZ arm, leading to study drug discontinuation on Day 6 was reported as three SAEs: ALT, AST and GGT, all three in one subject.
The SAEs of cholestatic hepatitis and the other of liver enzymes (ALT, AST and GGT) elevation are summarized below.

Subject ID (b) (6) – Country: Czech Republic

This patient was an 82-year-old male who on Day (b) (6) underwent surgery to remove a gastric tumor. He was intubated and treated for pneumonia from Days (b) (6) when study drug was discontinued due to cholestatic hepatitis. Maximum elevations of transaminases (ALT=88, AST=69) and alkaline phosphatase (250 U/L) were 2 times above the ULN and occurred on Day 6. Of note, total bilirubin peaked at baseline (10.4 micromol/L) prior to study drug administration. After discontinuation of study drug, transaminases and alkaline phosphatase

decreased and the AE was considered resolved on Day 16. The investigator considered this event as related to study medication.

M.O. comment: *The temporal relationship and the lack of other more probable causes of cholestatic hepatitis make this case likely to be associated with study drug, as the investigator concluded. Another fact that suggests association is the improvement observed when drug was discontinued. The list of concomitant medications did not include doses and frequency of administration to make a thorough evaluation, however, the list of drugs does not suggest a high probability of cholestatic hepatitis associated with their use.*

Subject ID: (b) (6) - Country: Spain

This patient was a 65-year-old female with the following relevant medical history: (1) Day (b) (6), the subject was hospitalized; (2) Day (b) (6), the subject had a subarachnoid hemorrhage and was intubated due to a GCS score of 3; and (3) Day (b) (6), the subject had an aneurysm repair and was transferred to the ICU. On Day-1, the subject was diagnosed with VABP and was treated for 6 days. On Day 6, the subject was diagnosed with SAEs of increased ALT (severe), increased AST (severe), and increased GGT (severe): ALT was 1492 IU/L (baseline: 57 IU/L; NR: 0-33 IU/L), AST was 1977 IU/L (baseline: 54 IU/L; NR: 14-34 IU/L), and GGT was 1326 IU/L (baseline and NR not available). Study medication was permanently discontinued due to these events on Day (b) (6). On the following day, an abdominal echography demonstrated a slightly globulous liver with diffusely increased echogenicity suggestive of steatosis but unable to identify focal lesions; permeable portal vein with hepato-portal flow; permeable suprahepatic veins; and permeable hepatic artery with resistances within NR. No treatment was administered for these events. On Day 8, the subject's AST was 228 IU/L and the following day, the event of increased AST was considered resolved. On Day 10, the subject's ALT was 525 IU/L and the event of increased ALT was considered resolved. On Day 20, the subject's GGT was 617 IU/L; this event was considered not resolved. The investigator considered the events of increased ALT, increased AST, and increased GGT to be SAEs that were not related to the study medication.
The subject completed the study on Day 61.

M.O. comment: *The temporal relationship with treatment and the improvement noted in the transaminases elevations after treatment discontinuation suggest a possible contribution of study drug to the development of ALT, AST and GGT elevations. Other potential contributing factors are liver steatosis and concomitant medications. It is difficult to evaluate the role of medications since doses and frequency of administration were not reported.*

Meropenem Arm:

Subject ID (b) (6) - Country: Czech Republic
Patient (b) (6) was a 68-year-old white male, with congestive heart failure and septic

shock. His medical history was relevant for diabetes. He received treatment with meropenem for 9 days for a diagnosis of VABP. Initially, amikacin and linezolid were administered concomitantly, and both stopped on Day 3. On day 9, his LFT results were: ALT 40, AST 102, total bilirubin 17.7 and ALP 73. LFT results met the laboratory criteria for Hy's Law (ALT or AST >3 × ULN, ALP ≤2.0 × ULN, and total bilirubin >2.0 × ULN) on Day (b) (6) days after the last dose of the study medication. On the same day, the subject died due to worsening of the SAE of septic shock.

M.O. comment: *This severely ill patient had septic shock on admission and met Hy's law laboratory criteria (b) (6) days after last dose of study drug treatment. At EOT, on day 9, his LFTs were not on a rising trend as compared to the day 3 results. A contribution of the study drug to the hepatotoxicity observed on day (b) (6), even though possible, is unlikely. The presence of diabetes and congestive heart failure along with the ongoing sepsis could have contributed to his hepatotoxicity.*

Subject ID (b) (6) – Country: Czech Republic

Patient (b) (6) was a 71-year-old white male who was hospitalized with chronic bronchitis, hypertension, and intestinal obstruction, secondary to a bowel carcinoma with peritoneal metastasis, for which he underwent a hemicolectomy. The subject experienced aspiration, septic shock and was transferred to the ICU and placed on mechanical ventilation. He was diagnosed with ventilated HABP and received a total of 7 days of therapy with meropenem, amikacin and linezolid from Days 1 to 2, at which time they were stopped. On Day 3, laboratory results met criteria for Hy's Law (ALT or AST >3 × ULN, ALP ≤2.0 × ULN, and total bilirubin >2.0 × ULN). On Day (b) (6), the subject was diagnosed with worsening septic shock, and died that same day. An autopsy was performed and confirmed multiple organ failure as the cause of death.

M.O. comment: *This elderly patient, with disseminated colon cancer, was severely ill post hemicolectomy, complicated with aspiration pneumonia. The ongoing sepsis along with the underlying oncologic disease make the assessment of the contribution of the study drug to his hepatotoxicity very difficult to evaluate. The contribution of the study drug to his hepatotoxicity is unlikely although it cannot be completely ruled out, given the temporal association of treatment. The drug exposure was very short (2 days) and the autopsy confirmed worsening septic shock as the cause of death. These two factors also suggest that the potential drug contribution is less likely than the underlying disease and co-morbidity.*

Subject ID (b) (6) – Country: Russia

Patient (b) (6) was an 81-year-old white female with a history of congestive heart failure and hypertension, admitted with an ischemic stroke. She was diagnosed with VABP and received a total of 15 days of treatment with meropenem, with linezolid, which was stopped on Day 4. Liver test results met the laboratory criteria for Hy's Law (ALT or AST >3 × ULN, ALP ≤2.0

× ULN, and total bilirubin >2.0 × ULN) on Day 15 (EOT), the same day as the last dose of the study medication. The patient completed the study, with last follow-up at day 43.

M.O. comment: *The temporal relationship with treatment and the decrease of LFTs elevations observed after completion of treatment, at day 43 of follow-up, indicate that a potential contribution of study drug to the hepatotoxicity cannot be ruled out. Confounding factors in the evaluation of causality include her underlying severe infection and congestive heart failure.*

Subject ID (b) (6) – Country: Germany

Patient (b) (6) was an 81-year-old white male with a history of renal failure and diabetes, diagnosed with VABP for which he received 9 days of meropenem treatment. At the EOT visit on the same day, the clinical response was assessed as "cure." On Day 20, 11 days after the last dose of the study medication, LFT results met the laboratory criteria for Hy's Law (ALT or AST >3 × ULN, ALP ≤2.0 × ULN, and total bilirubin >2.0 × ULN). On Day 25, the patient was diagnosed with multi-organ failure, which was the cause of death at Day (b) (6).

M.O. comment: *There was not a close temporal relationship to treatment in this patient, who had LFT elevations that met laboratory Hy's law criteria 11 days after the last dose of study medication. The presence of co-morbidities of renal failure and diabetes, and the ongoing infection, resulting in multi-organ failure are the most likely causes of the hepatotoxicity, observed (b) (6) days before her death.*

There were no cases of hepatic failure in the meropenem arm. One SAE of cholestatic hepatitis, considered "not resolved" was reported in one patient. A summary is presented below.

Subject ID (b) (6) – Country: Belgium

Patient (b) (6) was a 43-year-old white male, hospitalized on Day (b) (6) for multiple trauma injuries. On Day 1, the subject was diagnosed with VABP and meropenem was initiated. In addition, protocol-mandated adjunctive gram-positive therapy with linezolid (stopped on Day 3) was initiated. On Day 3, linezolid was de-escalated to flucloxacillin (Day 3 to Day 7). On Day 7, laboratory test results demonstrated an ALT of 115 U/L, AST of 101 U/L, total bilirubin of 2.1 (units not reported), ALP of 262 U/L, and GGT of 117 U/L (NRs not reported), and the subject was diagnosed with an SAE of severe cholestatic hepatitis. The study medication was permanently discontinued due to this event. The clinical response for VABP was assessed as "cure" at the EOT visit on Day 8 and the TOC visit on Day 15. On Day 8, laboratory test results demonstrated an ALT of 156 U/L (NR: 0-44 U/L), AST of 108 U/L (NR: 14-39 U/L), bilirubin of 34.5 µmol/L (NR: 5.1-20.5 µmol/L), and ALP of 305 U/L (NR: 53-129 U/L). On Day 31, laboratory test results demonstrated an ALT of 1025 U/L (NR: 0-44 U/L), ALP of 324 U/L (NR: 53-129 U/L), AST of 439 U/L (NR: 14-39 U/L), and bilirubin of 25.1 µmol/L (NR: 5.1-20.5 µmol/L). The event of cholestatic hepatitis was considered as not resolved. The investigator considered the event of

cholestatic hepatitis to be an SAE that was related to meropenem, as a possible relationship to either the IV meropenem or flucloxacillin could not be ruled out. All investigations to identify other causes of cholestatic hepatitis were negative. On day 31, the subject completed the study, and at the LFU visit (on Day 31), the clinical response was assessed as "sustained cure."

M.O. comment: *The concomitant treatment with flucloxacillin is a confounding factor. Meropenem cannot be excluded as a contributor to the development of severe cholestatic hepatitis in this patient, because of the temporal relationship and the known association of meropenem treatment with hepatic transaminase elevation. Flucloxacillin is a common cause of drug-induced liver injury in Europe, affecting approximately 8.5 in every 100,000 first time users of the drug (Andrews and Daly 2008).*

Renal Dysfunction

Overall, in PN008, a total of 32/361 (8.9%) TOL/TAZ and 22/359 (6.1%) meropenem patients had TEAEs related to renal dysfunction across the following preferred terms, belonging to the SMQ (narrow) Acute Renal Failure, in treatment and comparator arms, respectively: renal failure acute (4.7% vs 3.6%), renal failure (1.9% vs 0.6%)), renal impairment (1.4% vs 0.6%), azotaemia (1.1% vs 0.3%), oliguria (0.3% vs 1.1%), acute prerenal failure (0 vs 0.3%) and anuria (0 vs 0.6%). The table below shows a breakdown by treatment group and by individual PTs included in the SMQ Acute Renal Failure (narrow). The first row "Acute renal failure" shows the total number of patients (unique subject count) who contributed to one or more PTs included in this SMQ. If they contributed to more than one PT category, they are counted once in the first row.

Table 39. Adverse Events of Renal Dysfunction - Safety Population

		TOL/TAZ, N=361	Meropenem, N=359
Adverse Events	**AE Category**	**N (%)**	**N (%)**
Acute renal failure	**SMQ (narrow)**	**32 (8.9)**	**22 (6.1)**
Renal failure acute	PT	17 (4.7)	13 (3.6)
Renal failure	PT	7 (1.9)	2 (0.6)
Renal impairment	PT	5 (1.4)	2 (0.6)
Azotaemia	PT	4 (1.1)	1 (0.3)
Oliguria	PT	1 (0.3)	1 (0.3)
Acute prerenal failure	PT	0	1 (0.3)
Anuria	PT	0	2 (0.6)

At baseline, 27 of the 54 (50%) subjects with renal dysfunction TEAEs had abnormal creatinine clearance (<80 mL/min) (18/32 [56.3%] in the TOL/TAZ group vs. 9/22 [40.9%] in the meropenem group) and 21 (38.9%) had a medical history of a diagnosis in the renal and urinary disorders system organ class (SOC) (12 [37.5%] in the TOL/TAZ group vs. 9 [40.9%] in the meropenem group).

The number of patients with serious adverse events related to renal function were more frequent in the treatment arm [11 (3%)] relative to the comparator [4 (1.1%)]. These SAEs were reported as renal failure acute, in 9 (2.5%) TOL/TAZ recipients and in 3 (0.8%) of meropenem recipients, and renal failure in 2 (0.6%) TOL/TAZ recipients and in 1 (0.3%) meropenem recipient. As previously discussed, in the TOL/TAZ arm, 18/32 (56.2%) had mild, moderate, or severe impairment at baseline vs. 10/22 (40%) in the meropenem arm. A total of 11 of the 32 patients in the TOL/TAZ arm and 12 of the 22 in the meropenem arm had an outcome of recovered/resolved. However, because this trial enrolled severely ill patients, death was observed in approximately half of these patients. A total of 18 of the 32 (56.2%) subjects with renal dysfunction AEs in the TOL/TAZ and 10 of the 22 (45.5%) in meropenem arms died during the trial, due to complications of the infection and/or underlying conditions. All these patients who died had AEs of renal dysfunction that were ongoing at the time of death, except for 1 patient (# (b) (6) who had resolved renal failure (from days 2 to 5). Patients with unresolved/not recovered renal impairment events were 17 of 32 (53%) in the TOL/TAZ arm and 6 of 22 (27%) in the meropenem arm. One patient in the meropenem arm had an outcome of “fatal” associated with the renal impairment AE, not considered related to study drug by the investigator. A breakdown of the outcomes observed in patients with renal impairment AEs is presented by PT and treatment arm in Table 40 below. The lowest row summarizes the total number of patients in each category, using the safety population as the denominator to calculate percentages.

Table 40. Renal Impairment AEs Outcomes - Safety Population

	TOL/TAZ N=361				Meropenem N=359			
Dictionary Derived Term	**Not Recovered/ Not Resolved**	**Recovered/ Resolved**	**Recovering/ Resolving**	**Unknown**	**Fatal**	**Not Recovered/ Not Resolved**	**Recovered/ Resolved**	**Recovering/ Resolving**
Acute prerenal failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0	0 (0.0%)	1 (0.3%)	0 (0.0%)
Anuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0	0 (0.0%)	2 (0.6%)	0 (0.0%)
Azotaemia	2 (0.6%)	2 (0.6%)	0 (0.0%)	0	0	1 (0.3%)	0 (0.0%)	0 (0.0%)
Oliguria	1 (0.3%)	0 (0.0%)	0 (0.0%)	0	0	1 (0.3%)	3 (0.8%)	0 (0.0%)
Renal failure	5 (1.4%)	2 (0.6%)	0 (0.0%)	0	0	1 (0.3%)	0 (0.0%)	1 (0.3%)
Renal failure acute	8 (2.2%)	4 (1.1%)	3 (0.8%)	2 (0.6%)	1 (0.3%)	3 (0.8%)	6 (1.7%)	3 (0.8%)
Renal impairment	2 (0.6%)	3 (0.8%)	0 (0.0%)	0 (0.0%)	0	1 (0.3%)	1 (0.3%)	0 (0.0%)
Total number of subjects	17 (4.7%)	11 (3.0%)	3 (0.8%)	2 (0.6%)	1* (0.3%)	6 (1.7%)	12 (3.3%)	4 (1.1%)

*: This fatal event was not considered related to the study drug by the investigator. A total of 5 patients (3 in meropenem and 2 in TOL/TAZ) contributed to more than one event in this table. Source: ADAE, ADSL, Applicant's derived flags SAFFL, AEOUT

Ten of the 32 (31.3%) subjects in the TOL/TAZ group and 5 of the 22 (22.3%) subjects in the meropenem group with renal impairment/nephrotoxicity related AEs received renal replacement therapy (intermittent hemodialysis or peritoneal dialysis, continuous renal replacement therapy, continuous veno-venous filtration or Prismaflex), according to the Applicant's response to an inquiry. The Applicant noted that all renal replacement therapy occurred after study therapy had been discontinued or ended except for one case in the meropenem arm (Subject (b) (6)). A review of the database using the Applicant's derived flags in the ADCM, YP and ADSL datasets, showed that 10 (2.8%) patients in the TOL/TAZ and 5 (1.4%) in the meropenem groups received renal replacement therapy, due to development or worsening of renal impairment in temporal association with treatment.

Renal TEAEs leading to study drug withdrawal were also more frequent in the TOL/TAZ arm, 6 (1.7%) vs 1 (0.3%) in the meropenem arm. Among these 6 TOL/TAZ patients, end stage renal disease, defined as "developing CrCl <15 mL/min or oliguria <20 mL/24 h or dialysis or hemofiltration required while on treatment" as a reason for study drug discontinuation was reported in 3 (0.8%) patients in TOL/TAZ (patients # (b) (6), # (b) (6), # (b) (6)). The discontinuation of treatment followed protocol mandated criteria (section 7.5) to discontinue study drug when creatinine clearance fell <15 mL/min. These three patients were male, ages 63 to 84, and had received study drug for 4 to 7 days. Two of them had baseline creatinine clearance above 50 mL/min at baseline (Subject # (b) (6): CrCl 56.6 mL/min, Subject # (b) (6):92 mL/min) and one below 50 mL/min (CrCl:32.4 mL/min). All three were severely ill and had underlying conditions as confounding factors. Only 1 TEAE related to renal dysfunction (renal failure acute) in a meropenem treated subject (# (b) (6)) resulted in a subject's death (AE with fatal outcome), which was considered not related to study therapy by the investigator.

Subjects experiencing renal TEAEs in both treatment groups generally had significant comorbidities common in this patient population, which probably contributed to renal impairment. Diabetes as a co-morbidity was more frequent among patients in the TOL/TAZ arm who experienced renal impairment TEAEs and SAEs. Among patients who had TEAEs of renal failure, 13 of the 32 (40.6%) patients in TOL/TAZ arm and 2 of the 22 (9%) in the meropenem arm had diabetes. Among the patients who had SAEs of renal failure/impairment, 6 of the 11 patients in the TOL/TAZ arm had diabetes, and none of the 4 patients in the meropenem arm had diabetes. At baseline, 88/361 (24.4%) and 68/359 (18.9%) patients in TOL/TAZ and meropenem arms, respectively, had diabetes. Besides diabetic patients, other subgroups with higher reported rates of renal dysfunction/impairment TEAEs were patients older than 65 years, those with APACHE scores above 20 at baseline and creatinine clearance below 80 mL/min at baseline.

The distribution of TEAEs related to renal dysfunction/nephrotoxicity according to baseline characteristics and co-morbidities is presented below in Table 41 below.

Table 41. Subgroups With Higher Reported Rates of Adverse Events Related to Renal Impairment/Nephrotoxicity (Safety Population) - Medical Officer Table

Characteristic	Ceftolozane/Tazobactam N=361 n (%)	Meropenem N=359 n (%)
Age groups		
<65 years	13/201 (6.5)	9/202 (4.5)
>65 years	19/160 (11.9)	13/157 (8.3)
APACHE score grouping		
<20	14/237 (5.9)	13/245 (5.3)
>20	18/124 (14.5)	9/113 (7.9)
Creatinine clearance (CrCL) (mL/min)		
CrCL ≥80 mL/min	14/227 (6.2)	13/236 (5.5)
CrCL <80 mL/min	18/134 (13.4)	9/125 (7.2)
Diabetes diagnosis	13/88 (14.7)	2/68 (2.9)

TEAEs occurred at higher frequencies in patients with mild, severe, moderate and hyperclearance of baseline creatinine clearance relative to those with normal clearance, in both treatment arms. Higher rates of SAEs were observed in patients with baseline creatinine clearance <80 mL/min (pooled mild, moderate and severe impairment groups) in the TOL/TAZ arm, where 74 of 134 (55%) patients had SAEs compared with 58 of 124 meropenem patients (46.7%). Higher rates of SAEs in both arms were also observed in the hyperclearance at baseline group (>150 mL/min), representing critically ill patients with ongoing hyperdynamic cardiovascular conditions. In this group, 52 of 67 (77.6%) TOL/TAZ recipients had SAEs, compared to 41 of 64 (64%) meropenem recipients who had SAEs.

M.O. comment: *The rate comparisons of TEAEs among the 4 subgroups of renal impairment categories and between each treatment arm by category of baseline creatinine clearance have the limitation that they are based on relatively small groups of patients and the size of each group varied, with larger groups of patients in the normal baseline creatinine clearance category (in both treatment arms) as compared to the other groups.*

Treatment Emergent Adverse Events

Many of the reported TEAEs likely reflected the manifestations of disease under study, as well as, underlying comorbidities and concomitant therapies associated with critically ill patients with vHABP and VABP. A total of 310/361 (85.9%) and 299/359 (83.3%) of patients had at least one TEAE during the study in the treatment and comparator arms, respectively. The SOCs with higher rates, similar in both arms, were the Infections and Infestations (34.3% and 36.2% in treatment and comparator arm, respectively), followed by Gastrointestinal disorders (24.3% and 24.7% in treatment and comparator arm, respectively) and Respiratory, thoracic and mediastinal disorders (21% and 23.1% in treatment and comparator arm, respectively). The three SOCs with higher event rates in the treatment arm than in the comparator arm were the Investigations SOC (19.9% and 14.4%), Nervous System disorders (18.2% and 15.6%), and Renal and urinary disorders (13.5% and 11.1%). The PTs with higher rate differences in the

Investigations SOC were blood alkaline phosphatase increased (1.7% vs 0%), gamma-glutamyl transferase increased (1.4% vs 0). Other PTs with higher rates in the treatment arm in this SOC were hepatic transaminases increased, liver function test abnormal and blood bilirubin increased, and creatinine increased. In the Nervous System disorders SOC, the PTs that were driving the 2.6% difference in rates, higher in the treatment arm were cerebral hemorrhage (1.4% vs 0), encephalopathy (1.7% vs. 0.6%), convulsion (1.1% vs 0.8%), brain midline shift (1.1% vs 0.3%), hemorrhagic stroke (0.8% vs 0.3%), intracranial pressure increased (0.6% vs 0.3%) and quadriparesis (0.8% vs 0). In the Renal and urinary disorders SOC, the PTs with higher rate differences, higher in the treatment arm were: renal failure acute (4.7% vs. 3.6%), renal failure (1.9% vs. 0.6%), renal impairment (1.4% vs. 0.6%) and azotemia (1.1% vs. 0.3%).

The SOCs with higher rates and differences in the meropenem arm as compared to TOL/TAZ were: Blood and lymphatic disorders (19.2% vs. 14.4%), mainly driven by PTs of anemia and thrombocytopenia; Cardiac disorders (20% vs. 16.6%) with PTs of atrial fibrillation and tachycardia occurring more frequently in the meropenem arm; and Metabolism and nutrition disorders (16.4% vs. 13.0%), with hypokalemia, hypernatremia and hyponatremia occurring more frequently in the meropenem arm.

The Applicant presented an analysis of individual PTs occurring at a rate of 2% or higher in the safety population and displayed them in a Forest plot. The Applicant's analysis showed significant differences in *C. difficile* colitis, higher in the treatment arm [(8/361 (2.2%) for TOL/TAZ and 1/359 (0.6%) for meropenem] and thrombocytopenia, higher in the comparator arm [2/361 (0.6%) for TOL/TAZ and 17/359 (4.7%) for meropenem].

The Clinical reviewer evaluated all the MedDRA hierarchies including SMQs to guide a more detailed review of case reports and to summarize adverse events related to the same pathophysiological mechanism that were listed under different SOCs. The following SMQs had higher rates in the treatment arm, with highest risk differences with the treatment arm: Hepatic disorders (liver investigations, signs and symptoms), 16.3% vs 11.4%, Acute renal failure, 8.8% vs 6.6% and Cerebrovascular disorders, hemorrhagic cerebrovascular conditions 4.7% vs 2.2% and Pseudomembranous colitis, 10/361 or 2.77% vs 2/359 or 0.56%. The following PTs occurred only in the TOL/TAZ arm, at a rate of 1% or higher:

- Blood alkaline phosphatase increased, 6 vs. 0
- Cerebral hemorrhage, 5 vs. 0
- Metabolic acidosis, 5 vs. 0
- Gamma-glutamyl transferase increased, 5 vs. 0
- Urinary tract infection bacterial, 4 vs. 0
- Pneumonia aspiration, 4 vs. 0

<u>Hepatic disorders (liver investigations, signs and symptoms)</u>

Increases in liver transaminases were reported under more than one of the MedDRA Dictionary-derived terms (PTs). The lowest level term and verbatim term corresponding to these PTs were reviewed for accuracy by this medical officer. The PTs corresponding to elevation of liver transaminases were identified.

The following is a list of all PTs that reported elevations of liver enzymes:

- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood alkaline phosphatase increased
- Gamma-glutamyl transferase increased
- Hepatic enzyme increased
- Hypertransaminasaemia
- Liver function test abnormal

Most patients contributed to more than one PT in this category, because simultaneous increases of other transaminases are a common occurrence. Therefore, the use of the SMQ Hepatic disorders (liver investigations, signs and symptoms) complemented with a custom query with MAED allowed to count unique patients who contributed to one or more of these PTs related to liver enzymes. The following table shows the rates of the individual PTs under which increased liver transaminases were reported, and the top row shows the counts of unique subjects who contributed to one or more of these PTs (counted only once in this row) at any time during the study. The verbatim term reported and laboratory results from these patients were verified to confirm increased transaminases in all of them in one or more timepoints during the study.

Table 42. Customized Query "Hepatic Enzymes Increased" Results

Customized Query	**Ceftolozane/Tazobactam (TOL/TAZ) (N = 361)**		**Meropenem (N = 359)**	
Hepatic enzymes increased- MedDRA version 17.0, PTs included:	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Alanine aminotransferase increased	**48**	**13.3**	**26**	**7.2**
Aspartate aminotransferase increased				
Blood alkaline phosphatase increased				
Gamma-glutamyltransferase increased				
Hepatic enzyme increased				
Hypertransaminasaemia				
Liver function test abnormal				

Table 43. Rates of Individual PTs Under Which Increase of Liver Enzymes Were Reported

	Ceftolozane/Tazobactam (TOL/TAZ) (N = 361)		Meropenem (N = 359)	
Preferred Terms (PTs)	**Number of Subjects**	**Proportion (%)**	**Number of Subjects**	**Proportion (%)**
Alanine aminotransferase increased	21	5.82	14	3.9
Aspartate aminotransferase increased	19	5.26	14	3.9
Hepatic enzyme increased	10	2.77	7	1.95
Liver function test abnormal	7	1.94	2	0.56
Blood alkaline phosphatase increased*	6	1.66	0	0
Gamma-glutamyltransferase increased*	5	1.39	0	0
Hypertransaminasaemia	2	0.55	1	0.28

* the bold indicates those PTs that were only reported in one arm (the treatment arm)

A modified query was run to determine the rate of liver transaminases increased, excluding alkaline phosphatase and gamma-glutamyltransferase. The query, including the following PTs: *alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal,* yielded a total of 43 (11.9%) and 26 (7.2%) unique subjects who had contributed to one or more of these lists of selected PTs.

Medical Officer comment: *The rates of increased liver enzymes was numerically higher in the treatment arm. Increases in alkaline phosphatase and of gamma-glutamyltransferase were reported as PTs only in the treatment arm. In laboratory results of hepatic function tests, elevations of alkaline phosphatase were also more frequent and of higher fold-rise in the treatment arm, suggesting a trend of a cholestatic pattern in the treatment arm. The identification of all PTs under which these were reported allows for a count by unique patient IDs to avoid a false increase in rates and to provide a more accurate rate of elevation of hepatic enzymes in each treatment arm. I recommend reporting the rate of "hepatic transaminase increased" in the label as the number of unique patients reporting one or more of the PTs related to increases in transaminases: 43 (11.9%) and 26 (7.2%). All these individual patients were reviewed to confirm the presence of transaminases elevation in the laboratory results, corresponding to each PT.*

Acute Renal Failure

The incidence of acute renal failure was reviewed by exploring all the MedDRA terms under which it was reported. Using the SMQ Acute Renal Failure (narrow), the count of unique subjects contributing to one or more terms in this category was determined. The results are presented in the table below. The first row represents a count of unique subjects who contributed to one or more of the PTs in the table, and in the first row are counted only once.

Table 44. Acute Renal Failure – SMQ Rate and Individual Rates of Preferred Terms (PTs) Included

	TOL/TAZ N=361		Meropenem N=359	
MedDRA Categories	**N**	**%**	**N**	**%**
Acute renal failure [SMQ narrow]	32	8.9	22	6.1
Individual PTs included:				
Renal failure acute	17	4.7	13	3.6
Renal failure	7	1.9	2	0.6
Renal impairment	5	1.4	2	0.6
Azotaemia	4	1.1	1	0.3
Oliguria	1	0.3	4	1.1
Acute prerenal failure	0	0.0	1	0.3
Anuria	0	0.0	2	0.6

The SMQs that showed higher rates in the meropenem arm were the Hypersensitivity SMQs (7.0% in the meropenem arm and 5.3% in TOL/TAZ arm), Hematopoietic cytopenias (5.6% in the meropenem arm and 1.1% in the TOL/TAZ arm).

Events occurring only in the Meropenem arm at a rate of 1% or higher were:

- Bronchitis bacterial 6 vs 0
- Haemoptysis 4 vs 0

Please refer to Table 45 below, which shows the SOCs and PTs occurring at a rate of 1% and higher in any treatment arm.

Table 45. Treatment Emergent AEs Occurring at a Rate of 1% and Higher – Safety Population

Primary System Organ Class	**Ceftolozane/Tazobactam N= 309 (85.8%)**	**Meropenem N=298 (83.2%)**
Infections and infestations	**124 (34.3%)**	**130 (36.2%)**
Urinary tract infection	24 (6.6%)	25 (7.0%)
Septic shock	13 (3.6%)	17 (4.7%)
Sepsis	10 (2.8%)	4 (1.1%)
Clostridium difficile colitis	8 (2.2%)	1 (0.3%)
Pneumonia	7 (1.9%)	6 (1.7%)
Urinary tract infection fungal	6 (1.7%)	4 (1.1%)
Sinusitis	6 (1.7%)	4 (1.1%)
Tracheobronchitis	5 (1.4%)	3 (0.8%)
Urinary tract infection bacterial	4 (1.1%)	0 (0.0%)
Genitourinary tract infection	4 (1.1%)	5 (1.4%)
Cystitis	4 (1.1%)	5 (1.4%)
Bacteraemia	4 (1.1%)	6 (1.7%)
Gastrointestinal disorders	**88 (24.4%)**	**89 (24.8%)**
Diarrhoea	23 (6.4%)	25 (7.0%)
Vomiting	12 (3.3%)	10 (2.8%)
Constipation	8 (2.2%)	11 (3.1%)
Gastrointestinal haemorrhage	7 (1.9%)	6 (1.7%)
Gastritis erosive	6 (1.7%)	3 (0.8%)
Impaired gastric emptying	4 (1.1%)	3 (0.8%)
Nausea	4 (1.1%)	5 (1.4%)
Abdominal distension	4 (1.1%)	2 (0.6%)

Primary System Organ Class	Ceftolozane/Tazobactam N= 309 (85.8%)	Meropenem N=298 (83.2%)
Respiratory, thoracic and mediastinal disorders	**76 (21.1%)**	**83 (23.1%)**
Hydrothorax	16 (4.4%)	20 (5.6%)
Respiratory failure	10 (2.8%)	9 (2.5%)
Pneumothorax	8 (2.2%)	7 (1.9%)
Pleural effusion	8 (2.2%)	10 (2.8%)
Pulmonary embolism	7 (1.9%)	5 (1.4%)
Atelectasis	5 (1.4%)	5 (1.4%)
Acute respiratory distress syndrome	5 (1.4%)	3 (0.8%)
Pneumonia aspiration	4 (1.1%)	0
Investigations	**72 (19.9%)**	**52 (14.5%)**
Alanine aminotransferase increased	21 (5.8%)	14 (3.9%)
Aspartate aminotransferase increased	19 (5.3%)	14 (3.9%)
Transaminases increased	11 (3.0%)	10 (2.8%)
Hepatic enzyme increased	10 (2.8%)	7 (1.9%)
Liver function test abnormal	7 (1.9%)	2 (0.6%)
Blood alkaline phosphatase increased	6 (1.7%)	0 (0.0%)
Gamma-glutamyltransferase increased	5 (1.4%)	0 (0.0%)
Blood bilirubin increased	4 (1.1%)	2 (0.6%)
Blood creatinine increased	4 (1.1%)	3 (0.8%)
Nervous system disorders	**66 (18.3%)**	**56 (15.6%)**
Brain oedema	9 (2.5%)	11 (3.1%)
Encephalopathy	6 (1.7%)	2 (0.6%)
Cerebral haemorrhage	5 (1.4%)	0 (0.0%)
Brain midline shift	4 (1.1%)	1 (0.3%)
Convulsion	4 (1.1%)	3 (0.8%)
Cardiac disorders	**60 (16.6%)**	**72 (20.1%)**
Atrial fibrillation	9 (2.5%)	16 (4.5%)
Cardiac failure acute	9 (2.5%)	8 (2.2%)
Cardiac arrest	8 (2.2%)	6 (1.7%)
Cardiac failure	8 (2.2%)	3 (0.8%)
Tachycardia	7 (1.9%)	9 (2.5%)
Bradycardia	5 (1.4%)	7 (1.9%)
Cardio-respiratory arrest	5 (1.4%)	4 (1.1%)
Skin and subcutaneous tissue disorders	**54 (15.0%)**	**50 (13.9%)**
Decubitus ulcer	25 (6.9%)	17 (4.7%)
Skin ulcer	7 (1.9%)	8 (2.2%)
Subcutaneous emphysema	4 (1.1%)	1 (0.3%)
Urticaria	4 (1.1%)	3 (0.8%)
Blood and lymphatic system disorders	**52 (14.4%)**	**69 (19.2%)**
Anaemia	32 (8.9%)	38 (10.6%)
Thrombocytosis	5 (1.4%)	7 (1.9%)
Anaemia of chronic disease	5 (1.4%)	2 (0.6%)
Renal and urinary disorders	**49 (13.6%)**	**40 (11.1%)**
Renal failure acute	17 (4.7%)	13 (3.6%)
Polyuria	8 (2.2%)	5 (1.4%)
Renal failure	7 (1.9%)	2 (0.6%)
Renal impairment	5 (1.4%)	2 (0.6%)
Azotaemia	4 (1.1%)	1 (0.3%)
General disorders and administration site conditions	**49 (13.6%)**	**51 (14.2%)**
Multi-organ failure	14 (3.9%)	10 (2.8%)
Pyrexia	12 (3.3%)	8 (2.2%)

Primary System Organ Class	Ceftolozane/Tazobactam N= 309 (85.8%)	Meropenem N=298 (83.2%)
Metabolism and nutrition disorders	**47 (13.0%)**	**59 (16.4%)**
Hypokalaemia	12 (3.3%)	16 (4.5%)
Hypoalbuminaemia	7 (1.9%)	5 (1.4%)
Hypernatraemia	6 (1.7%)	10 (2.8%)
Metabolic acidosis	5 (1.4%)	0 (0.0%)
Hyponatraemia	4 (1.1%)	10 (2.8%)
Hypoglycaemia	4 (1.1%)	9 (2.5%)
Hyperkalaemia	4 (1.1%)	5 (1.4%)
Hyperglycaemia	4 (1.1%)	3 (0.8%)
Vascular disorders	**35 (9.7%)**	**46 (12.8%)**
Hypotension	15 (4.2%)	18 (5.0%)
Hypertension	4 (1.1%)	10 (2.8%)
Injury, poisoning and procedural complications	**26 (7.2%)**	**23 (6.4%)**
Post procedural haemorrhage	4 (1.1%)	4 (1.1%)
Psychiatric disorders	**22 (6.1%)**	**31 (8.6%)**
Delirium	7 (1.9%)	6 (1.7%)
Agitation	5 (1.4%)	11 (3.1%)
Hepatobiliary disorders	**11 (3.0%)**	**20 (5.6%)**
Surgical and medical procedures	**9 (2.5%)**	**5 (1.4%)**
Tracheostomy	7 (1.9%)	3 (0.8%)
Eye disorders	**7 (1.9%)**	**5 (1.4%)**
Musculoskeletal and connective tissue disorders	**6 (1.7%)**	**7 (1.9%)**
Ear and labyrinth disorders	**5 (1.4%)**	**1 (0.3%)**
Endocrine disorders	**4 (1.1%)**	**1 (0.3%)**
Reproductive system and breast disorders	**4 (1.1%)**	**3 (0.8%)**

Laboratory Findings

The number of patients with missing baseline laboratory values was small (less than 10%) and comparable between treatment arms. Post-baseline laboratory values were adequate in number and frequency to conduct a review. Overall, elevations of 1 to 3 times the ULN in liver transaminases and bilirubin were observed in approximately half of all patients and were comparable between treatment arms. Elevations of transaminases ≥5 times the ULN were also comparable between treatment arms. ALT elevations ≥5 times the ULN were observed in a total of 40/361 (11.1%) of TOL/TAZ patients and in 47/359 (13%) of meropenem recipients. AST elevations ≥5 times the ULN were observed in 39/361 (10.8%) of TOL/TAZ patients and in 37/359 (10.3%) of meropenem recipients.

Higher rates of alkaline phosphatase elevations 3 times the ULN were observed in the TOL/TAZ arm vs. the meropenem arm (8.86% vs 4.46% elevations). The table below shows the increases in liver laboratory values post-baseline by levels above the upper limit of normal.

Table 46. Liver Laboratory Tests Post-Baseline - Safety Population

Liver Lab Test	Ceftolozane/Tazobactam N=361			Meropenem N=359		
ALT≥ULN	**Event Count**	**Subject Count**	**% of Subjects**	**Event Count**	**Subject Count**	**% of Subjects**
2x ULN	216	115	31.86	225	122	33.98
3x ULN	111	66	18.28	111	66	18.38
5x ULN	46	29	8.03	52	33	9.19
10x ULN	10	8	2.22	11	10	2.79
20x ULN	3	3	0.83	4	4	1.11
AST≥ULN	**Event Count**	**Subject Count**	**% of Subjects**	**Event Count**	**Subject Count**	**% of Subjects**
2x ULN	171	104	28.81	210	124	34.54
3x ULN	89	59	16.34	81	58	16.16
5x ULN	31	26	7.20	36	29	8.08
10x ULN	11	9	2.49	6	6	1.67
20x ULN	5	4	1.11	2	2	0.56
ALP≥ULN	**Event Count**	**Subject Count**	**% of Subjects**	**Event Count**	**Subject Count**	**% of Subjects**
2x ULN	140	67	18.56	87	50	13.93
3x ULN	44	32	8.86	19	16	4.46
5x ULN	5	5	1.39	5	4	1.11
10x ULN	1	1	0.28	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
TB≥ULN	**Event Count**	**Subject Count**	**% of Subjects**	**Event Count**	**Subject Count**	**% of Subjects**
1.5x ULN	32	19	5.26	30	18	5.01
2x ULN	19	9	2.49	15	9	2.51
3x ULN	15	7	1.94	8	7	1.95

Source: ADSL and LB datasets, using sponsor-derived flags. All scores are post-baseline. Subject scores may be counted more than once in that they will be counted in all conditions (i.e., 2x, 3x, 5x…) that apply.

The maximum increases in liver laboratory tests were comparable between treatment arms. The tables below show the maximum increases by baseline values and times above the ULN.

Table 47. Maximum Shifts of Alanine Aminotransferase Values From Baseline - Safety Population

	Ceftolozane/Tazobactam (N=361) ALT Baseline										Meropenem (N=359) ALT Baseline									
	ALT <2x ULN		2x ≤ ALT <5x ULN		5x ≤ ALT <10x ULN		10x ≤ ALT <20x ULN		ALT ≥20x ULN		ALT <2x ULN		2x ≤ ALT <5x ULN		5x ≤ ALT <10x ULN		10x ≤ ALT <20x ULN		ALT ≥20x ULN	
ALT Maximum	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
ALT<2x ULN	209	57.9	11	3.0	1	0.3	0	0.0	0	0.0	196	54.6	7	1.9	0	0.0	0	0.0	0	0.0
2x≤ALT<5x ULN	**69**	**19.1**	12	3.3	2	0.6	0	0.0	0	0.0	63	17.5	19	5.3	0	0.0	0	0.0	0	0.0
5x≤ALT<10x ULN	**10**	**2.8**	**9**	**2.5**	1	0.3	0	0.0	0	0.0	8	2.2	11	3.1	2	0.6	1	0.3	1	0.3
10x≤ALT<20x ULN	**2**	**0.6**	**2**	**0.6**	**0**	**0.0**	0	0.0	0	0.0	5	1.4	1	0.3	0	0.0	0	0.0	0	0.0
ALT≥20x ULN	**3**	**0.8**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	0	0.0	3	0.8	1	0.3	0	0.0	0	0.0	0	0.0

n, Subject count.
Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the subject counts, therefore, percents may not add up to 100.

Table 48. Maximum Shifts of Aspartate Aminotransferase Values From Baseline - Safety Population

	Ceftolozane/Tazobactam (N=361) AST Baseline										Meropenem (N=359) AST Baseline									
	AST <2x ULN		2x ≤ AST <5x ULN		5x ≤ AST <10x ULN		10x ≤ AST <20x ULN		AST ≥20x ULN		AST < x2 ULN		2x ≤ AST <5x ULN		5x ≤ AST <10x ULN		10x ≤ AST <20x ULN		AST ≥20x ULN	
AST Maximum	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
AST<2x ULN	218	60.4	14	3.9	2	0.6	0	0.0	0	0.0	179	49.9	19	5.3	1	0.3	1	0.3	0	0.0
2x≤AST<5x ULN	**50**	**13.9**	20	5.5	2	0.6	0	0.0	0	0.0	59	16.4	27	7.5	3	0.8	0	0.0	0	0.0
5x≤AST<10x ULN	**10**	**2.8**	**6**	**1.7**	0	0.0	0	0.0	0	0.0	18	5.0	4	1.1	1	0.3	0	0.0	0	0.0
10x≤AST<20x ULN	**3**	**0.8**	**1**	**0.3**	**0**	**0.0**	0	0.0	1	0.3	4	1.1	0	0.0	0	0.0	0	0.0	0	0.0
AST≥20x ULN	**4**	**1.1**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	0	0.0	2	0.6	0	0.0	0	0.0	0	0.0	0	0.0

n, Subject count.
Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the subject counts, therefore, percents may not add up to 100.

Table 49. Maximum Shifts of Alkaline Phosphatase Values From Baseline - Safety Population

	Ceftolozane/Tazobactam (N=361) ALP Baseline										Meropenem (N=359) ALP Baseline									
	ALP<2x ULN		2x ≤ ALP <5x ULN		5x ≤ ALP <10x ULN		10x ≤ ALP <20x ULN		ALP≥20x ULN		ALP< x2 ULN		2x ≤ ALP <5x ULN		5x ≤ ALP <10x ULN		10x ≤ ALP <20x ULN		ALP≥20x ULN	
ALP Maximum	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
ALP<2x ULN	274	76	4	1.1	0	0.0	0	0.0	0	0.0	284	79.1	4	1.1	0	0.0	0	0.0	0	0.0
2x≤ALP<5x ULN	**45**	**12**	15	4.2	0	0.0	0	0.0	0	0.0	33	9.2	11	3.1	0	0.0	0	0.0	0	0.0
5x≤ALP<10x ULN	**4**	**1**	**0**	**0.0**	0	0.0	0	0.0	0	0.0	2	0.6	1	0.3	0	0.0	0	0.0	0	0.0
10x≤ALP<20x ULN	**1**	**0**	**0**	**0.0**	**0**	**0.0**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALP≥20x ULN	**0**	**0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

n, Subject count.
Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the subject counts, therefore, percents may not add up to 100.

Table 50. Maximum Shifts of Total Bilirubin Values From Baseline - Safety Population

	Ceftolozane/Tazobactam (N=361) TB Baseline										Meropenem (N=359) TB Baseline									
	TB <2x ULN		2x ≤ TB <5x ULN		5x ≤ TB <10x ULN		10x ≤ TB <20x ULN		TB ≥20x ULN		TB < x2 ULN		2x ≤ TB <5x ULN		5x ≤ TB <10x ULN		10x ≤ TB <20x ULN		TB ≥20x ULN	
TB Maximum	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
TB<2x ULN	322	89.2	1	0.3	0	0.0	0	0.0	0	0.0	308	85.8	1	0.3	0	0.0	0	0.0	0	0.0
2x≤TB<5x ULN	**5**	**1.4**	0	0.0	0	0.0	0	0.0	0	0.0	6	1.7	0	0.0	0	0.0	0	0.0	0	0.0
5x≤TB<10x ULN	**2**	**0.6**	**2**	**0.6**	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0
10x≤TB<20x ULN	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	0	0.0	0	0.0	1	0.3	0	0.0	1	0.3	0	0.0	0	0.0
TB ≥20x ULN	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

n, Subject count.
Note: Subjects who have only baseline visit information or who were missing a baseline visit but had post baseline visits were not included in the subject counts, therefore, percents may not add up to 100.

Renal function laboratories

Creatinine and creatinine clearance increase from baseline throughout the study follow-up were comparable between treatment arms. The tables below show increases in creatinine and in creatinine clearance by baseline categories.

Table 51. Creatinine Maximum Shifts Post-Baseline

Baseline Toxicity Grade Creatinine (umol/L)	Maximum Toxicity Grade	Ceftolozane/Tazobactam N=343	Meropenem N=337
Normal	0	256 (74.6%)	256 (75.7%)
	1	11 (3.2%)	18 (5.3%)
	2	20 (5.8%)	11 (3.3%)
	3	2 (0.6%)	3 (0.9%)
Grade 1	0	8 (2.3%)	10 (3.0%)
	1	9 (2.6%)	9 (2.7%)
	2	7 (2.0%)	5 (1.5%)
	3	1 (0.3%)	0 (0.0%)
Grade 2	0	0 (0.0%)	3 (0.9%)
	1	7 (2.0%)	2 (0.6%)
	2	15 (4.4%)	16 (4.7%)
	3	6 (1.7%)	2 (0.6%)
Grade 3	2	0 (0.0%)	1 (0.3%)
	3	1 (0.3%)	1 (0.3%)

Source: ADSL, ADLB, subjects without post-baseline laboratory values are not included

Table 52. Creatinine Clearance Maximum Shifts From Baseline

Baseline CrCL Category	Max pBL CrCL Category	Ceftolozane/ Tazobactam N=220	Meropenem N=215
Baseline Stage 1: ≥90 (Normal or High)	Stage 1: ≥90 (Normal or High)	98 (27.1%)	110 (30.6%)
	Stage 2: 60-89 (Mild)	19 5.3%)	18 (5.0%)
	Stage 3: 30-59 (Moderate)	4 (1.1%)	7 (1.9%)
	Stage 4: 15-29 (Severe)	1 (0.3%)	2 (0.6%)
Baseline Stage 2: 60-89 (Mild)	Stage 1: ≥90 (Normal or High)	28 (7.8%)	30 (8.4%)
	Stage 2: 60-89 (Mild)	39 (0.8%)	25 (7.0%)
	Stage 3: 30-59 (Moderate)	11 (3.0%)	8 (2.2%)
	Stage 4: 15-29 (Severe)	2 (0.6%)	3 (0.8%)
Baseline Stage 3: 30-59 (Moderate)	Stage 1: ≥90 (Normal or High)	6 (1.7%)	7 (1.9%)
	Stage 2: 60-89 (Mild)	20 (5.5%)	13 (3.6%)
	Stage 3: 30-59 (Moderate)	36 (0.0%)	27 (7.5%)
	Stage 4: 15-29 (Severe)	8 (2.2%)	7 (1.9%)
	Stage 5: <15 (Kidney Failure)	1 (0.3%)	0 (0.0%)
Baseline Stage 4: 15-29 (Severe)	Stage 2: 60-89 (Mild)	3 (0.8%)	3 (0.8%)
	Stage 3: 30-59 (Moderate)	11 (3.0%)	8 (2.2%)
	Stage 4: 15-29 (Severe)	9 (2.5%)	11 (3.1%)
	Stage 5: <15 (Kidney Failure)	0 (0.0%)	1 (0.3%)

Vital Signs

The mean changes in pulse, temperature, and systolic and diastolic blood pressure from baseline across scheduled visits were small and similar between the 2 treatment groups.

Electrocardiograms (ECGs)

Electrocardiograms were not a mandated protocol procedure, they were done as needed for clinical care and routine monitoring of patients admitted to intensive care units.

QT

This study did not evaluate QT prolongation. In a randomized, placebo-controlled crossover thorough QTc study, 51 healthy subjects were administered a single therapeutic dose (1.5 g) and a supra-therapeutic dose (4.5 g) of ceftolozane/tazobactam. Exposure to ceftolozane/tazobactam did not significantly affect heart rate, electrocardiogram morphology, PR, QRS, or QT interval. Therefore, it was concluded that ceftolozane/tazobactam does not affect cardiac repolarization.

Immunogenicity

This section is not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

The following safety issues were identified in the review:

8.2.5.1. Worsening or Recurring Intracranial Hemorrhages

There were a total of 23 cases of worsening intracranial hemorrhages or brain herniation, 17 in TOL/TAZ and 6 in the meropenem arm, most of them fatal. Confirmed worsening or recurrent intracranial hemorrhages were 16 in the TOL/TAZ arm and 5 in the meropenem arm. These occurred in severely ill patients, most of them with predisposing factors such as recent or ongoing cerebrovascular disorders or head trauma. While there was a small imbalance between treatment arms at baseline in the number of patients with predisposing factors for intracranial hemorrhage, it does not rule out an association with drug use. This imbalance at baseline was not substantial or proportional to the rate differences observed in intracranial hemorrhages between treatment arms. Please refer to the corresponding safety review sections (deaths, serious adverse events).

8.2.5.2. Nephrotoxicity

There were higher rates of renal impairment AEs in this trial as compared to the cUTI and cIAI trials. The trial population in PN008 reflects a more severely ill and older population. Also, the

dose of TOL/TAZ is higher and the duration of treatment is longer for HABP/VABP than for the cUTI and cIAI indications. Serious adverse events of impairment of renal function were more frequent in the TOL/TAZ arm (1.7% vs 0.3%), and three patients in the TOL/TAZ arm discontinued treatment because of development of end-stage renal disease that required dialysis treatment. Please refer to the "significant events of special interest" section for more details.

8.2.5.3. Hepatotoxicity

Two cases of laboratory criteria for Hy's law and two cases of liver failure which did not meet laboratory criteria for Hy's law were reported among patients who received TOL/TAZ during this trial. The rate of transaminase increases observed in this trial were higher than those observed in the cUTI and cIAI trial. The two cases of hepatic failure with fatal outcomes and the two non-fatal serious adverse events related to hepatotoxicity were reported in severely ill patients treated with TOL/TAZ, who had additional confounders for liver toxicity (a case of cholestatic hepatitis and a case of increased transaminases that led to study drug discontinuation, with an outcome of "unresolved"). In the meropenem arm, there were no fatal hepatic failure cases, there was one case of cholestatic hepatitis in a severely ill patient, with an outcome of resolution. In addition, there were 4 patients who met laboratory criteria for Hy's law in the meropenem arm. Please refer to the significant events of special interest for more details.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Because of the nature of the disease and relevant endpoints, there were no patient reported outcomes assessed in the studies to support the HABP/VABP indication.

8.2.7. Safety Analyses by Demographic Subgroups

Overall, the distribution of AEs among the age cohorts was characterized by an increased frequency of AEs in the older populations in the Phase 3 study, with a tendency towards a higher frequency of SAEs in the older patients in both treatment arms. The rate differences between treatment and comparator arm were wider in the older cohorts, and higher in the treatment arm as compared with the meropenem arm. The subgroup of patients with renal impairment also showed higher rates of AEs, and particularly higher rates of SAEs, in both arms. The subgroups are small to make adequate comparisons, and some of the baseline creatinine clearance categories of renal impairment show a 10% higher rate in the TOL/TAZ arm, but others have a similar or lower rate as compared to the meropenem arm. Overall, rates are comparable between treatment arms in patients with renal impairment at baseline.

The table below shows the rates of TEAEs and SAEs by baseline creatinine clearance categories.

Table 53. TEAEs by Baseline Creatinine Clearance Categories

	TEAE Rates by Baseline CrCl	
Baseline Creatinine Clearance Categories	**TOL/TAZ**	**Meropenem**
>50 - <80 mL/min (mild impairment)	72/82 (87.8%)	62/77 (80.5%)
≥15 - <30 mL/min (severe impairment)	16/17 (94.1%)	20/21 (95.2%)
≥150 mL/min (hyperclearance)	56/67 (83.6%)	46/64 (71.9%)
≥30 - ≤50 mL/min (moderate impairment)	33/35 (94.3%)	24/26 (92.3%)
≥80 - <150 mL/min (normal)	133/160 (83.1%)	147/171 (86.0%)

Table 54. SAEs by Baseline Creatinine Clearance Categories

Baseline Creatinine Clearance Categories	SAE Rates by Baseline CrCl	
	TOL/TAZ	**MEROPENEM**
>50 - <80 mL/min (mild impairment)	43/82 (52.4%)	30/77 (38.9%)
≥15 - <30 mL/min (severe impairment)	10/17 (58.8%)	15/21 (71.4%)
≥150 mL/min (hyperclearance)	20/67 (29.8%)	15/64 (23.4%)
≥30 - ≤50 mL/min (moderate impairment)	21/35 (60%)	13/26 (50%)
≥80 - < 150 mL/min (normal)	59/160 (36.8%)	56/171 (32.7%)

Another subgroup analyzed by the Clinical reviewer is that of patients with a diagnosis of diabetes at baseline. There was an increased rate of SAEs, particularly of renal failure/impairment in this population, and events related to renal failure in diabetic patients occurred more frequently in the treatment arm than in the meropenem arm. A total of 10/361 (2.8%) TOL/TAZ and 3/359 (0.8%) meropenem recipients who had diabetes (as baseline flag) had reported renal failure/impairment related PTs (acute prerenal failure, renal disorder, renal failure, renal failure acute, renal failure chronic and renal impairment). Of these, 6 (1.7%) were SAEs and all of them occurred in the TOL/TAZ arm, 0 in the meropenem arm.

Table 55. Overall Summary of Treatment Emergent Adverse Events by Age Category (<65 and ≥65) - Safety Population

	<65 years old		≥65 years old	
Adverse Event Category	**Ceftolozane/ Tazobactam N=201 n (%)**	**Meropenem N=202 n (%)**	**Ceftolozane/ Tazobactam N=160 n (%)**	**Meropenem N=157 n (%)**
Any TEAE	165 (82.1)	164 (81.2)	145 (90.6)	135 (86.0)
Any SAE	69 (34.3)	59 (29.2)	83 (51.9)	70 (44.6)
Any TEAE leading to discontinuation of study drug	19 (3.0)	22 (10.9)	18 (11.3)	20 (12.7)
TEAE that resulted in death	43 (21.4)	40 (19.8)	62 (38.8)	61 (38.9)

Source: ADAE, ADSL, age group 2, safety population, Applicant's treatment emergent flag

Table 56. Overall Summary of Treatment Emergent Adverse Events by Age Category (<75 and >75) - Safety Population

TEAE category	<75 years: Ceftolozane/tazobactam N= 278 n (%)	<75 years: Meropenem N= 284 n (%)	≥75 years: Ceftolozane/tazobactam N= 83 n (%)	≥75 years: Meropenem N=75 n (%)
Any TEAE	235 (84.5%)	236 (83.1%)	75 (90.4%)	63 (84.0%)
Any Serious TEAE	106 (38.1%)	94 (33.1%)	46 (55.4%)	35 (46.7%)
Results in Death	66 (23.7)	70 (24.6)	39 (46.9)	31 (41.3)

Source: ADAE, ADSL, age group 3, safety population

Table 57. Overview of Adverse Events Distribution by Sex - Safety Population

	Males		Females	
Types of Adverse Events	TOL/TAZ N= 261 n (%)	Meropenem N= 252 n (%)	TOL/TAZ N= 100 n (%)	Meropenem N=107 n (%)
TEAEs	221 (84.7)	210 (83.3)	89 (89)	89 (83.2)
SAEs	102 (39.1)	91 (36.1)	50 (50)	38 (35.5)
Results in death	71 (27.2)	66 (26.1)	34 (34)	35 (32.7)
Leading to drug withdrawal	26 (9.9)	31 (12.3)	11 (11)	11 (10.2)

Source: ADAE, ADSL, safety population, Applicant's treatment emergent flag

Conclusions about the distribution of TEAEs by gender is limited by the much smaller size in the female subgroup (N=207) as compared to males (N=513) in the safety population. Rates of TEAEs were comparable in males and females of the meropenem arm, and relatively higher in females of the TOL/TAZ arm as compared to males in the same treatment arm.
Proportionally higher rates of SAEs were observed in females of the TOL/TAZ arm (50%) as compared to those of the meropenem arm (35.5%). The proportion of TEAEs resulting in death was relatively higher in females than in males, in both treatment arms, and slightly higher in the TOL/TAZ arm as compared to the meropenem arm.
Not done yet!

8.2.8. Specific Safety Studies/Clinical Trials

This section is not applicable to this NDA supplement, as no specific safety study has been conducted in relation to the indication sought.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The relatively short duration of therapy and treatment follow-up (up to 30 days) in the Phase 3 trial largely precluded a meaningful evaluation of oncologic events. A review of the SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) for the pooled phase 3 studies previously conducted (cIAI and cUTI) showed a total of 2 cases (1 adrenal adenoma

and 1 bladder cancer) in the TOL/TAZ arm and 2 cases (colon cancer and renal cancer) in the pooled comparator arm. In the HABP/VABP study, a total of 3 cases of benign tumors were reported in the whole study population, distributed as follows: one case of frontal lobe hygroma, benign, was reported in the TOL/TAZ arm and 2 cases of malignant neoplasia in the meropenem arm, a case of malignant peritoneal neoplasia and a case of renal cancer. Because of the relatively short treatment and other clinical characteristics, it is the Clinical reviewer's assessment that these cases are unrelated to study drug exposure.

Human Reproduction and Pregnancy

Pregnancy

Pregnant and lactating women were excluded from eligibility in all TOL/TAZ studies that have been conducted to date. The Applicant provided a review of the literature through May 15, 2018 from EMBASE and did not identify any published observational studies that evaluated the use of ceftolozane and/or tazobactam during pregnancy. According to the Applicant, "a cumulative search of the worldwide company database identified a total of 1 spontaneous, prospective pregnancy exposure report and no non-interventional reports". No details, such as maternal age, timing of exposure, etc., were available for this case. The outcome was reported as "pending".

The Division consulted with the DPMH and another literature search was performed in February 2019. A single publication regarding tazobactam use in pregnancy was identified and is summarized below.

The publication title was, "Influence of pregnancy on the pharmacokinetic behavior and the transplacental transfer of the piperacillin-tazobactam (PPR-TZB) combination,"(Bourget et al. 1998) and included six patients. Evidence was found of an increase in volume of distribution and clearance during pregnancy. The therapeutic consequence of these events is that maternal circulating levels of PPR-TZB were, by 4 h, less than the MIC of target organisms (i.e., ≤8 mcg/mL) both on Day 1 and at steady state. Currently, there are no data available on Zerbaxa use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. The available published information accumulated for several decades has not identified an association between cephalosporin use during pregnancy and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups. Available nonclinical studies do not suggest concern for adverse fetal outcomes.

Lactation

No relevant data were found in the published literature on lactation, pregnancy or development, after a search was conducted on PubMed, EMBASE, Micromedex, LactMed and *"Medications and Mother's Milk"*. There are no data on the presence of ceftolozane in human milk, the effects on the breastfed infant, or the effects on milk production. Tazobactam is present in human milk. There are no data on the effects of tazobactam on the breastfed infant,

or the effects on milk production. In general, cephalosporins as a class are considered safe for breastfeeding mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOL/TAZ and any potential adverse effects on the breastfed infant from TOL/TAZ or from the underlying maternal condition.

Females and Males of Reproductive Potential

There are no new studies on reproductive and developmental toxicology effects of TOL/TAZ. No published literature was identified regarding the effect of Zerbaxa on fertility in humans. No adverse effects on fertility were seen in animals.

For details on preclinical studies and results, please refer to the Pharmacology/Toxicology review by Dr. James Wild, PhD.

(b) (4)

Current Status of PREA required studies for cUTI and cIAI indications:

Pediatric studies were required under the Pediatric Research and Equity Act (PREA) at the time of initial NDA approval for cUTI and cIAI indications. These postmarketing requirements (PMR) are as follows, both of which are currently ongoing:

PMR 2809-1 Conduct a randomized, double-blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem

in hospitalized children from birth to <18 years with cUTI. Current enrollment as of December 19, 2018: 59 of 120 patients have been randomized.
Final study report submission date: 31 DEC 2020.

PMR 2809-2 Conduct a randomized, double-blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI. Current enrollment as of December 19, 2018: 43 of 120 patients have been randomized.
Final study report submission date: 31 DEC 2020.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Beta-lactams and beta-lactam inhibitor combinations are not known to be associated with abuse potential, withdrawal symptoms or rebound.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

As of April 2, 2019, there are 381 reports associated with TOL/TAZ in the FAERS database, retrieved with Empirica Study by the Clinical reviewer. A review of these events showed that most PTs are consistent with current safety labeling. A causality assessment is precluded by missing or incomplete data and the presence of confounding factors in these reports.

Expectations on Safety in the Postmarket Setting

Safety monitoring in the post-marketing setting will continue. A post-marketing study of platelet function is recommended. Surveillance for the emergence of resistance, and adverse events will be monitored. Emergence of new safety events can be managed by routine pharmacovigilance surveillance.

8.2.11. Integrated Assessment of Safety

The safety database to support the HABP/VABP indication includes a total of 361 subjects who received ceftolozane/tazobactam (TOL/TAZ) at the proposed marketed dose of 3 g q8h in the Phase 3 Study PN008. In addition, 71 subjects enrolled in three Phase 1 studies were exposed to a 3 g (or CrCL-adjusted) dose of TOL/TAZ, of whom 37 received a single dose and 34 received multiple (up to 28) doses. In Study PN008, a total of 726 critically-ill subjects were randomized, of whom 361 received 3 g q8h TOL/TAZ (or CrCL-adjusted dose) and 359 received 1 g q8h of meropenem. A total of 6 of the randomized subjects, 2 in the TOL/TAZ arm and 4 in the meropenem arm, did not receive study drug and were not included in the safety population. Approximately two-thirds of the patients were male and had a diagnosis of VABP. All patients in the study were ventilated at randomization, 49.3% for more than 5 days, and had a median APACHE score of 17.

Patients with an APACHE score >20 at baseline represented 32.9% of the population. Key comorbid conditions at baseline (e.g., chronic obstructive pulmonary disease, diabetes, congestive heart failure) were similar between the treatment groups.

The majority (63%) of subjects received between 8 and 14 days of study therapy, with a comparable mean duration of exposure in both treatment groups; 20.7% of subjects received less than the specified minimum treatment course of 8 days. An additional 16.3% of overall subjects received 14 days of therapy. The median duration of exposure was 7.7 days in both treatment arms.

A high proportion of patients in this critically-ill population in both treatment groups experienced TEAEs (84.6%), including a substantial proportion of subjects who experienced serious TEAEs (39.0%) and fatal TEAEs (28.6%). The mortality rates throughout the whole study follow-up period beyond Day 28 were higher in the TOL/TAZ arm by 1%, with rates of 29.1% in TOL/TAZ and 28.1% in the meropenem arm.

The incidence of serious TEAEs was higher in the TOL/TAZ group (42.1%) compared to the meropenem group (35.9%).

The leading cause of death in the TOL/TAZ arm was cerebrovascular hemorrhagic events. Recurring or worsening of intracranial hemorrhages were three-fold higher in the treatment arm, representing the highest risk difference among fatal events between the two arms (4.4% vs 1.1%). The imbalance could not be attributed to significant baseline differences in medical history between treatment arms. Most of these patients, in both arms, had predisposing cerebrovascular conditions or head trauma, and no clear relationship to thrombocytopenia or prothrombin time was found in most cases. Different confounding factors for increased risk of worsening or recurring hemorrhages were present in some of these patients, without a defined common pattern in all. Hemorrhages in other body sites were not significantly increased.

Beta-lactams may increase risks of hemorrhages in more than one way. Thrombocytopenia, hypoprothrombinemia and platelet aggregation dysfunction have been described in association with several beta-lactams and cephalosporins. Platelet dysfunction, previously described with beta-lactams, including piperacillin-tazobactam, was not evaluated in the study. It is also biologically plausible that TOL/TAZ may be a contributing factor to platelet dysfunction, by inducing abnormalities in platelet aggregation. Platelet dysfunction can be present without alterations of platelet counts, PT or PTT values, and may be evident only by a prolongation of the bleeding time. It can last several days after study drug discontinuation. Therefore, there is biological plausibility that TOL/TAZ may contribute to worsening of hemorrhages and this risk cannot be confirmed or excluded based on the available data from these patients. The biological plausibility has been demonstrated with dechallenge and positive rechallenge with piperacillin-tazobactam, further strengthening the evidence. The size of the risk difference (three-fold higher in the treatment arm) in the absence of substantial baseline differences in risk factors among treatment arms, and the temporal association are two additional criteria that support a potential study drug contribution to these events. Individuals with cerebrovascular disease or recent neurosurgical procedures or trauma appear to be at higher risk for worsening or recurrent intracranial hemorrhages in the TOL/TAZ arm than in the meropenem arm. Platelet function studies were not performed with TOL/TAZ in this or in any

previous study. This warrants labeling and postmarketing requirements consideration. A total of 16/17 cases in the TOL/TAZ arm and 4/6 in the meropenem arm resulted in fatal outcomes. The lack of a second study to assess the reproducibility of these findings is a limitation in the assessment of causality.

The following drug class related adverse events were observed during the trial in higher frequencies in the TOL/TAZ arm as compared to meropenem: *C. difficile*-associated diarrhea (2.8% vs 0.6%) and post-baseline seroconversion of the Coombs test (30.2% vs 3.5%) without increased incidence of anemia. Hypersensitivity events were not observed at an increased rate in the TOL/TAZ arm as compared to the meropenem arm. No serious hypersensitivity reactions needing study drug discontinuations were reported during the study. A total of 5.3% subjects in the TOL/TAZ arm and 7.0% in meropenem arm reported one or more events of terms indicating cutaneous or systemic allergic reactions.

The safety profile in this study was also characterized by higher rates of events related to nephrotoxicity/renal impairment in both treatment arms (8.9% in TOL/TAZ and 6.1% in meropenem). Resolution of renal failure/impairment was observed in 11 of 32 (34%) of the TOL/TAZ treated patients and in 12/22 (54%) meropenem treated patients. Patients with lower creatinine clearance at baseline, the elderly and those with diabetes were a high-risk group for nephrotoxicity. Serious adverse events of renal failure and study drug discontinuations due to development of end-stage renal disease and requiring renal replacement therapy were more frequent in the TOL/TAZ arm. Mortality due to progression of disease and/or complications of the underlying conditions was high in this subgroup, and higher in the TOL/TAZ arm (18 of 32 of 53% in the TOL/TAZ arm and 10 of 22 or 27% patients in the meropenem arm).

Increases in transaminases and alkaline phosphatase were observed in approximately half of the patients with normal baseline values, in similar proportions to those of the meropenem arm. Alkaline phosphatase elevations were more frequent in the TOL/TAZ arm. Hy's law laboratory criteria were met in 2 and 4 patients with preexisting liver conditions in TOL/TAZ and meropenem arms, respectively. Two events of liver failure without Hy's law laboratory criteria reported in severely ill patients with underlying liver conditions were observed in the TOL/TAZ arm. In addition to these cases with fatal outcomes, two serious adverse events of hepatotoxicity were reported in TOL/TAZ recipients: one case of cholestatic hepatitis and one of severe elevations of liver transaminases and GGT. These cases had an outcome of unresolved/not fully resolved up to the end of the study follow-up. One case of cholestatic hepatitis was reported as a serious adverse event in the meropenem arm, with an outcome of resolved. All these patients in both arms were severely ill and had underlying co-morbidities as confounders. It is not possible to confirm or to exclude a potential contribution of TOL/TAZ, by direct toxicity or indirectly by lack of efficacy, to these serious hepatotoxicity events. They were numerically higher in the TOL/TAZ arm and complete resolution was not observed in any of the cases of the TOL/TAZ arm.

In this study, the more severely ill population is a likely contributor to the increased toxicities observed in HABP/VABP as compared to the cUTI and cIAI. Several differences between the study populations of HABP/VABP are worth mentioning: for example, in the cIAI trial, patients were younger (median age of 52), and had a median APACHE II score of 7. The daily dose was

half of that administered in the HABP/VABP trial, and the duration of therapy was lower overall (median of 6 days). All these factors probably influenced the changes observed in the adverse event profile of TOL/TAZ in the new proposed indication of HABP/VABP. The limitations to the generalizability of the study conclusions from a safety perspective are the following:

- Limited enrollment of non-white patients and relatively small number of females as compared to males
- Limited enrollment of patients with severe renal impairment and no data for patients with baseline ESRD on hemodialysis
- No clinical trial data for pregnant or lactating patients
- No clinical trial data for patients with severe immune deficiencies (HIV, neutropenia, transplant patients)

Cross-Discipline Team Leader Assessment:

(b) (4)

Based on FDA guidance, to include an adverse event in the Warnings and Precautions section of the label, "…there should be reasonable evidence of a causal association between the drug and the adverse event…" While there were numerical imbalances in some of the subgroups, such a finding is expected with multiple analyses. The patients enrolled in Trial P008 had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20 equating to a predicted mortality rate of 35% or higher.[2] Attribution of these adverse events to study therapy is difficult given the high severity of illness of the patients, their underlying infections and other critical illnesses, complications related to co-morbid conditions, and multiple concomitant medications.

With particular regard to the observed intracranial hemorrhage adverse events, it is also noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites. Additionally, there is no evidence from the literature that TOL/TAZ causes platelet dysfunction.

These safety issues can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with these adverse events. Additionally, patients with HABP/VABP are typically closely monitored, often in an intensive care unit, and any decrement in renal or hepatic function can be detected.

[2] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

Please refer to Section 1.3 of this review for additional details.

8.3. Statistical Issues

There are no major statistical issues that impact the overall conclusions. Minor statistical issues were mentioned and addressed throughout Section 8.

8.4. Conclusions and Recommendations

A single Phase 3 trial (PN008) was conducted to evaluate the efficacy and safety of ceftolozane/tazobactam for the treatment of VABP/vHABP.

Overall the Applicant has provided substantial evidence of effectiveness of ceftolozane/tazobactam for the treatment of VABP/vHABP. The results of PN008 demonstrate noninferiority of ceftolozane/tazobactam to meropenem in the Day 28 all-cause mortality rate. Results for the key secondary endpoint of clinical response at the TOC visit showed similar results for the two treatment arms. Sensitivity analyses and various subgroup analyses demonstrated that the primary analysis findings were robust.

The safety database allowed for an adequate assessment of the safety profile in this severely ill patient population, characterized by increased rates of fatal and serious adverse events in the treatment arm as compared to the control. No significant baseline differences or imbalances in confounding factors were present between treatment arms to fully explain the differences observed. Higher rates of events of nephrotoxicity, hepatotoxicity, and worsened or recurrent intracranial hemorrhages in severely ill patients with additional risk factors were observed at higher rates in the treatment arm as compared to the control. The lack of a second study to assess the reproducibility of these findings is a limitation to the safety assessment. The risk of worsening or recurrent intracranial hemorrhages, observed to be three-fold higher in the treatment arm, warrants further post marketing studies of the study drug's effect on platelet function, and continuous monitoring of events of hemorrhages, renal and hepatic toxicity. Safety risks can be managed by adequate labeling information, to include warnings and precautions for serious and fatal adverse events observed in the HABP/VABP trial.

The limitations to the generalizability of the study conclusions are the following:

- Limited enrollment of non-white patients and relatively small number of females as compared to males
- Limited enrollment of patients with severe renal impairment and no data for patients with baseline ESRD on hemodialysis
- No clinical trial data for pregnant or lactating patients
- No clinical trial data for patients with severe immune deficiencies (HIV, neutropenia, transplant patients)

Clinical-Discipline Team Leader Assessment:

(b) (4)

Based on FDA guidance, to include an adverse event in the Warnings and Precautions section of the label, "…there should be reasonable evidence of a causal association between the drug and the adverse event…" While there were numerical imbalances in some of the subgroups, such a finding is expected with multiple analyses. The patients enrolled in Trial P008 had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20 equating to a predicted mortality rate of 35% or higher.[3] Attribution of these adverse events to study therapy is difficult given the high severity of illness of the patients, their underlying infections and other critical illnesses, complications related to co-morbid conditions, and multiple concomitant medications.

With particular regard to the observed intracranial hemorrhage adverse events, it is also noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites. Additionally, there is no evidence from the literature that TOL/TAZ causes platelet dysfunction.

These safety issues can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with these adverse events. Additionally, patients with HABP/VABP are typically closely monitored, often in an intensive care unit, and any decrement in renal or hepatic function can be detected.

Please refer to Section 1.3 of this review for additional details.

[3] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

9 Advisory Committee Meeting and Other External Consultations

There were no issues in the sNDA that needed discussion at an Advisory Committee Meeting or other external consultation.

10 Pediatrics

There are no clinical data available with TOL/TAZ in the pediatric HABP/VABP population.

(b) (4)

(b) (4)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
Safety section updates have been proposed to the current label regarding (b) (4) intracranial hemorrhages. The labeling was not finalized at the time of the completion of this review.

Because of the serious risks observed in Trial PN008, and the availability of risk mitigation strategies that can be lifesaving and help prescribers make their own risk-benefit assessment for individual patients, this reviewer recommends adding the following warnings and precautions, (b) (4) Hematological adverse events, including platelet dysfunction are included in a warning of the current piperacillin-tazobactam label, therefore, the inclusion of these adverse events is also consistent with drug class labeling and with current labeling of tazobactam as part of the combination piperacillin-tazobactam (Zosyn).

These recommendations are made following current FDA Guidance for Industry on *"Warnings and Precautions, contraindications, and Boxed Warning sections of Labeling for Human Prescription Drug and Biological Products - Content and Format, October 2011"* and taking into consideration the guiding principles from Attachment B: Clinical Safety Review of an NDA or BLA, MAPP 6010.3 Rev. 1, Section 7.3:

5.2 Nephrotoxocity in the HABP/VABP clinical trial
In the HABP/VABP trial, nephrotoxicity has been reported with ZERBAXA and with the comparator, in higher rates than in the cUTI and cIAI trials, especially in those with renal impairment, those with co-morbidities such as diabetes, the elderly and those receiving concomitant nephrotoxic medications. Serious events of renal failure and study drug discontinuations due to development of end-stage renal disease and requiring hemodialysis were more frequent in the ZERBAXA arm. *[see Adverse Reactions 6.1]* Assess CrCl in all patients prior to initiating therapy, daily during therapy, and adjust doses accordingly. *[see Dosage and Administration (2.2)].*

5.3 Hepatotoxicity in the HABP/VABP clinical trial

In the HABP/VABP trial, liver failure with fatal outcome has been reported in severely ill HABP/VABP ZERBAXA treated patients with severe pre-existing liver conditions or co-morbidities. Approximately half of patients with normal hepatic transaminases at baseline experienced maximum increases in ALT or AST between 1 to 5 times the upper level of normal (ULN). Increases of ALT or AST equal or greater than 5 times the ULN were observed in patients with normal baseline values in 2% of patients. Careful patient selection, management of concomitant medications with known or potential hepatotoxicity and more frequent monitoring of liver enzymes and hepatic function are recommended when using ZERBAXA for the HABP/VABP indication.

5.4 Worsening of Intracranial Hemorrhage in the HABP/VABP clinical trial

In the HABP/VABP trial, worsening of intracranial bleeding, with fatal outcomes, has been reported in 17/361 ZERBAXA treated patients and in 6/359 meropenem treated subjects, who were severely ill and had known predisposing factors such as ongoing or recent cerebrovascular traumatic injury or stroke, liver or renal failure. There were no imbalances in risk factors between the two treatment arms. Platelet dysfunction, reported with other beta-lactams, has not been assessed in these patients during the study. The benefit of ZERBAXA treatment in patients with ongoing or recent intracranial bleeding has not been demonstrated and its use should be limited when no other options are available. If ZERBAXA is used in these patients, hematological monitoring for risk of bleeding, including assessment of bleeding time, is recommended before and during treatment, and discontinuation of treatment if increased risks are observed.

Cross-Discipline Team Leader Assessment:

(b) (4)

Based on FDA guidance, to include an adverse event in the Warnings and Precautions section of the label, "…there should be reasonable evidence of a causal association between the drug and the adverse event…" While there were numerical imbalances in some of the subgroups, such a finding is expected with multiple analyses. The patients enrolled in Trial P008 had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline APACHE II score of ≥20 equating to a predicted mortality rate of 35% or higher.[4] Attribution of these adverse events to study therapy is difficult given the high severity of illness of the patients, their underlying infections and other critical illnesses, complications related to co-morbid conditions, and multiple concomitant medications.

With particular regard to the observed intracranial hemorrhage adverse events, it is also noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4

[4] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites. Additionally, there is no evidence from the literature that TOL/TAZ causes platelet dysfunction.

These safety issues can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with these adverse events. Additionally, patients with HABP/VABP are typically closely monitored, often in an intensive care unit, and any decrement in renal or hepatic function can be detected.

Please refer to Section 1.3 of this review for additional details.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary, and the risks of Zerbaxa may be adequately managed in the post-marketing setting through labeling. Post-marketing safety requirements and monitoring recommendations will be made.

13 Postmarketing Requirements and Commitment

(b) (4)

Safety

Because of the safety risk of worsening and/or recurrent intracranial hemorrhages observed in the Phase 3 study to support the HABP/VABP indication, and the limited preclinical and clinical experience with the proposed dose of 3g Q 8 hours, the Clinical reviewer recommends a clinical study in healthy volunteers, per recommendations from the FDA Division of Hematology, to study the effect of TOL/TAZ on platelet function. This recommendation is also based on the conclusions from the two hematologist consultants that reviewed the cases of intracranial hemorrhages for the Applicant.

Cross-Discipline Team Leader Assessment:

(b) (4)

Based on FDA guidance, to include an adverse event in the Warnings and Precautions section of the label, "…there should be reasonable evidence of a causal association between the drug and the adverse event…" While there were numerical imbalances in some of the subgroups, such a finding is expected with multiple analyses. The patients enrolled in Trial P008 had a high severity of illness with a median APACHE II score of 17, and 32.9% of subjects had a baseline

APACHE II score of ≥20 equating to a predicted mortality rate of 35% or higher.[5] Attribution of these adverse events to study therapy is difficult given the high severity of illness of the patients, their underlying infections and other critical illnesses, complications related to co-morbid conditions, and multiple concomitant medications.

With particular regard to the observed intracranial hemorrhage adverse events, it is also noted that TOL/TAZ was approved on 12/29/2014 for the treatment of cUTI and cIAI at a dose of 1.5 g (1.0 g ceftolozane/0.5 g tazobactam) every 8 hours, with a treatment duration ranging from 4 to 14 days. A review of the FAERS database by the Office of Surveillance and Epidemiology did not identify a signal for increased hemorrhagic adverse events in the CNS or at other body sites. Additionally, there is no evidence from the literature that TOL/TAZ causes platelet dysfunction.

These safety issues can be adequately communicated in Section 6 (Adverse Reactions). Routine post-marketing surveillance should be sufficient to assess for any trends associated with these adverse events. Additionally, patients with HABP/VABP are typically closely monitored, often in an intensive care unit, and any decrement in renal or hepatic function can be detected.

Please refer to Section 1.3 of this review for additional details.

[5] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818-29.

14 Division Director (DAIP) Comments

Please see my comments in Section 1.3.

15 Appendices

15.1. References

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15.2. Financial Disclosure

A total of 47 investigators, one of whom is now deceased, have not been certified regarding the Absence of Financial Interests and/or Arrangements. The Division requested that Merck provide an assessment of the number of patients enrolled by these 47 investigators and the impact this could have on the overall study results. If certification had not yet been obtained, Merck would have had to provide a sensitivity analysis of the primary endpoint excluding these patients.

Merck responded that there was a total of 98 subjects enrolled/randomized across 23 sites where at least one investigator was missing a Financial Disclosure Form. This included 6 subjects enrolled in Phase 1 studies and 92 patients enrolled in the Phase 3 pivotal study, PN008.

Merck provided an update on February 21, 2019 on the status of Financial Disclosure Form completion. At that point, 16 of the 47 investigators had provided financial disclosure forms (12 Merck forms and 4 similar forms from the CRO) indicating no conflict of interest. Additionally, for 15 (32%) investigators, Merck's further review of study documentation confirmed that the investigator either did not participate in the study or participation did not coincide with subject enrollment. For the remaining 11 (23%) investigators whose participation in the study coincided with subject enrollment, Merck stated that a total of 16 subjects (6 in the TOL/TAZ arm and 10 in the meropenem arm) had been enrolled at these investigators' sites and performed a sensitivity analysis of the primary endpoint excluding these subjects.

The results of the sensitivity analysis were consistent with the primary endpoint of All-Cause Mortality in the Intent-to-Treat (ITT) population.

Covered Clinical Study (Name and/or Number): Study P008 (CXA-NP-11-04)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 853		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 47		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

A separate nonclinical review will be provided related to labeling.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Individual Study Reviews

Study 7625A-018 (CXA-EB-13-05): A Phase 1 study to evaluate the pharmacokinetics, safety, and tolerability of ceftolozane-tazobactam IV in adult Japanese, Chinese, and Caucasian Healthy subjects.

In this study, each subject received a single dose of 1.5 g ceftolozane (1g) -tazobactam (0.5 g), followed by a 48 hours washout period, and then a single dose of 3 g ceftolozane (2 g) -

tazobactam (1 g). The plasma PK parameters of ceftolozane and tazobactam for each ethnicity are presented in Table 58.

Table 58. Plasma Pharmacokinetics of Single Dose of 3 g Ceftolozane-Tazobactam

	Caucasian	Chinese	Japanese
N	10	8	9
Ceftolozane		Geometric Mean (CV%)	
C_{max} (µg/mL)	134 (11.6)	133 (5.6)	132 (8.1)
$AUC_{0-\infty}$ (µg·h/mL)	337 (15.2)	295 (10.7)	292 (11.9)
$t_{1/2}$ (h)	2.2 (16.0)	1.9 (7.7)	1.8 (8.4)
Fraction excreted (%)	61.5 (21.2)	71.4 (21.0)	56.5 (65.7)
Tazobactam		Geometric Mean (CV%)	
C_{max} (µg/mL)	32.2 (16.3)	29.4 (11.1)	32.7 (12.2)
$AUC_{0-\infty}$ (µg·h/mL)	43.9 (19.0)	38.2 (14.4)	41.5 (14.1)
$t_{1/2}$ (h)	0.64 (10.5)	0.59 (8.6)	0.58 (6.0)
Fraction excreted (%)	55.7 (48.3)	64.9 (51.7)	49.8 (160.2)

The ceftolozane and tazobactam AUCs tend to be higher in Caucasian subjects compared to Asian (Japanese and Chinese) subjects. However, the differences do not appear to be clinically significant.

Study 007MK7625A: A Phase 1, prospective, multi-center, open-label study to assess the plasma pharmacokinetics and lung penetration of IV ceftolozane-tazobactam in critically-ill patients.

Ceftolozane-tazobactam doses evaluated in this study are summarized in Table 59.

Table 59. Summary of Study Groups and Dosing

Group	Renal Function (mL/min)	Number of Patients	Dose (g)	Route, Frequency, Duration	Total Number of Doses
Group 1; ventilated pneumonia patients	CLcr>50	21	3	IV q8h (±1h) as a 60±10-minute infusion	4-6
	CLcr 30 to 50	4	1.5		
	CLcr 15 to 29	1	0.75		6
Group 2: Critically ill patients	CLcr≥180	10	3	IV once as a single 60 ± 10-minute infusion	Single-dose

Group 1

In Group1, ELF fluid for determination of ceftolozane and tazobactam concentrations was collected at 1, 2, 4, 6, or 8 hours after the start of the infusion of the last dose. The plasma and ELF PK parameters of ceftolozane and tazobactam are presented in Table 60.

Table 60. Ceftolozane and Tazobactam Plasma and ELF Pharmacokinetic Parameters at First and Last Dose in Ventilated Patients With Proven or Suspected Pneumonia

Ceftolozane						
PK parameter	Plasma				ELF[a]	
	First Dose		Last Dose		Last dose	
	N	GM	N	GM	N	Mean
AUC_{0-8} (µg·h/mL)¥	24	248 (203-301)	23	394 (323-481)	22	154
C_{max} (µg/mL)¥	25	73 (61.4-86.9)	24	100 (84.2-120)	22	27.4
CL (L/h)†	24	4.9 (64.1)	23	4.5 (67.7)	--	N/A
V_{ss} (L)†	24	27.5 (29.9)	23	29.4 (45.5)	--	N/A
Tazobactam						
PK parameter	Plasma				ELF[a]	
	First Dose		Last Dose		Last dose	
	N	GM	N	GM	N	Mean
AUC_{0-8} (µg·h/mL)¥	25	51.3 (41.3-63.9)	23	61.9 (49.6-77.2)	22	27.5
C_{max} (µg/mL)¥	25	22.6 (18.9-27.1)	24	26.1 (21.8-31.3)	22	5.37
CL (L/h)†	25	15.0 (68.5)	23	14.1 (75.6)	--	N/A
V_{ss} (L)†	25	39.9 (28.9)	23	40.4 (38.8)	--	N/A

[a] Individual ELF concentrations from 22 patients were pooled and averaged to estimate the pooled ELF PK parameters
¥ Statistics for AUC_{0-8} and C_{max}, geometric mean and 95% confidence interval
† Statistics for CL and V_{ss}: GM and GCV% = 100*sqrt(exp(s2)-1), where s2 is the observed between-subjects variance on the natural log-scale
CI = Confidence interval; GCV = geometric coefficient of variation; GM = Geometric least-squares mean; NA = Not applicable

The lung penetration in ELF in ventilated patients with proven or suspected pneumonia when using the unbound last dose AUC_{0-8} for ceftolozane and tazobactam was ~50% and 63%, respectively. These drug penetrations for ceftolozane and tazobactam in patients are comparable to ceftolozane and tazobactam penetrations in healthy subjects at ~60% and 63%, respectively.

Group 2

Group 2 consisted of 10 critically ill patients (APACHE II score range of 12-35) with CLcr > 180 mL/min. ELF fluid was not collected in Group 2. The plasma PK parameters of ceftolozane and tazobactam are presented in Table 60.

The plasma PK parameters of ceftolozane and tazobactam are presented in Table 61.

Table 61. Ceftolozane and Tazobactam Plasma Pharmacokinetics of a Single 3 G Dose in Critically Ill Patients With Augmented Renal Function (ARF)

	Ceftolozane		Tazobactam	
Plasma PK parameter	N	GM	N	GM
AUC_{0-8} (µg·h/mL)¥	10	188 (139-256)	10	31.1 (20.3-47.6)
C_{max} (µg/mL)¥	10	68.9 (55.0-86.5)	10	17.4 (13.5-22.5)
CL (L/h)†	10	8.98 (57.6)	9	28.7 (67.9)
V_{ss} (L)†	10	30.2 (41.1)	9	51.6 (41.1)

¥ Statistics for AUC_{0-8} and C_{max}, geometric mean and 95% confidence interval
† Statistics for CL and V_{ss}: GM and GCV% = 100*sqrt(exp(s2)-1), where s2 is the observed between-subjects variance on the natural log-scale
CI = Confidence interval; GCV = Geometric coefficient of variation; GM = Geometric least-squares mean; NA = Not applicable

When comparing the ceftolozane C_{max} and AUC_{0-8} values from HABP/VABP patients with CLcr values between 80-150 mL/min to that of patients with ARF, the C_{max} and AUC_{0-8} values in HABP/VABP patients were 49% and 97% higher, respectively, than the values in ARF patients. For tazobactam, the C_{max} and AUC_{0-8} values from HABP/VABP patients with CLcr 80-150 mL/min were 99% and 48% higher, respectively, than that of ARF patients. While the C_{max} and AUC_{0-8} values differed greatly between the two groups, it should be noted that the AUC_{0-8} and C_{max} values in ARF patients were calculated after a single dose of ceftolozane-tazobactam versus after steady state in the patients with CLcr 80-150 mL/min. Despite the differences in ceftolozane and tazobactam AUC_{0-8} and C_{max} values between patients in both groups, all patients in the ARF group had ceftolozane exposures that achieved > 70% plasma *f*T>MIC at MIC values of 4 and 8 µg/mL, and tazobactam exposures that achieved 60% plasma *f*T>1 µg/mL.

Study 008MK7625A: A Phase 3, prospective, randomized, double-blind, multi-center, study to assess the safety and efficacy of IV ceftolozane-tazobactam in adult patients with HABP/VABP.

In this study, the safety and efficacy of IV ceftolozane-tazobactam 3 g IV every 8 hours were evaluated compared with meropenem 1 g IV every 8 hours in adult patients with HABP/VABP.

Plasma PK samples were collected from 305 patients out of 322 patients enrolled in the ceftolozane-tazobactam arm after multiple dose administrations of ceftolozane-tazobactam. A total of 1481 and 1455 plasma concentrations of ceftolozane and tazobactam, respectively, were used for the population PK analyses. Most samples were excluded from the analysis, because they were above or below the concentration limits. The plasma PK parameters of ceftolozane and tazobactam are presented in Table 62.

Table 62. Ceftolozane and Tazobactam Plasma Pharmacokinetics in HABP/VABP Patients

	Ceftolozane	Tazobactam
Plasma PK parameter	GM (GCV%)	GM (GCV%)
AUC_{0-8} (µg·h/mL)	341 (55.2)	56.1 (73.7)
C_{max} (µg/mL)	96.1 (43.3)	24.2 (41.6)
CL (L/h)	5.85 (55.5)	17.8 (73.9)
V_{ss} (L)	25.8 (42.1)	42.0 (30.9)

GCV% = Geometric coefficient of variation; GM = Geometric least-squares mean

15.4.2. Pharmacometrics Review

Population Pharmacokinetic (POP PK) Modeling Review

The Applicant used their previously submitted POP PK models of ceftolozane (TOL) and tazobactam (TAZ)—CUBI-PCS-100 and CXA-POPPK-002—to develop two updated POP PK models that were submitted with this current sNDA:

- W2J: Population Pharmacokinetic Analysis of Ceftolozane and Tazobactam (MK-7625A) for CXA-ICU-14-01 (MK7625A PN007)
- ZC7: Population Pharmacokinetic Analysis for Ceftolozane and Tazobactam (MK-7625A) in Adult Patients with Ventilated Nosocomial Pneumonia

In addition to including TOL and TAZ plasma concentration data from patients with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and nosocomial pneumonia (NP), model W2J incorporated concentration data collected from epithelial lining fluid (ELF) while model ZC7 incorporated concentration data collected in patients with end-stage renal disease (ESRD). The source of data for each model is elaborated in Table 63.

Table 63. Studies Included in POP PK Models W2J and ZC7.

Study Number/Phase	Study Title	Models
CXA-101-01/ Phase 1	A Phase 1, Randomized, Double-blind, Placebo-controlled, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Intravenous Ceftolozane (CXA-101) in Healthy Adult Subjects	W2J, ZC7
CXA-101-02/ Phase 1	A Phase 1, Open-label, Pharmacokinetic, Safety, and Tolerability Study of a Single Intravenous Dose of CXA-101 in Subjects with Normal Renal Function or Mild Renal Impairment	W2J, ZC7
CXA-101-03/ Phase 2	A Multicenter, Double-blind, Randomized, Phase 2 Study to Compare the Safety and Efficacy of Intravenous CXA-101 and Intravenous Ceftazidime in Complicated Urinary Tract Infection, Including Pyelonephritis	W2J, ZC7
CXA-201-01/ Phase 1	A Phase 1, Randomized, Double-blind, Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous CXA-101, Tazobactam, and CXA-101/Tazobactam Administered to Healthy Adult Subjects	W2J, ZC7
CXA-201-02/ Phase 1	A Phase 1, Open-label, Pharmacokinetic, Safety, and Tolerability Study of a Single Intravenous Dose of CXA-101/Tazobactam in Subjects with Normal Renal Function or Mild or Moderate Renal Impairment	W2J, ZC7
CXA-MD-11-07/ Phase 1	A Phase 1, Randomized, Placebo-Controlled, Multi-dose, Double-blind Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous CXA-201 Administered to Healthy Adult Subjects	W2J, ZC7
CXA-QT-10-02/ Phase 1	A Double-Blind, Double-Dummy, Randomized, Moxifloxacin and Placebo Controlled, Four-Way Crossover Study of the Effects of a Single Intravenous Supra-Therapeutic Dose and a Single Intravenous Therapeutic Dose of CXA-101/Tazobactam on the QT/QTc Intervals in Healthy Subjects	W2J, ZC7
CXA-ELF-10-03/ Phase 1	Prospective, Open-label, Multiple-dose Intrapulmonary Pharmacokinetic Study of Intravenous CXA-201 (CXA-101/Tazobactam) and Piperacillin/ Tazobactam to Evaluate the Pulmonary Penetration and Safety of CXA-201 in Healthy Adult Volunteers	W2J, ZC7
CXA-REN-11-01/ Phase 1	Prospective, Open-Label, Pharmacokinetic Study of Intravenous CXA-201 in Subjects With Severe Renal Impairment and End Stage Renal Disease Requiring Hemodialysis	W2J, ZC7
CXA-IAI-10-01/ Phase 2	A Multicenter, Double-Blind, Randomized, Phase 2 Study to Compare the Safety and Efficacy of Intravenous CXA-101/ Tazobactam and Metronidazole with that of Meropenem in the Treatment of Complicated Intraabdominal Infections	W2J, ZC7
CXA-DDI-12-10/ Phase 1	A Phase 1 Drug-Drug Interaction Study to Evaluate the Potential of Ceftolozane/Tazobactam to Influence the Pharmacokinetics of CYP1A2, CYP3A4 and OAT1/OAT3 Probe Substrate Drugs in Healthy Subjects	W2J, ZC7
CXA-EB-13-05/ Phase 1	A Single-dose, Open-label, Parallel-group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ceftolozane/Tazobactam Administrated Intravenously to Adult Japanese, Chinese, and Caucasian Healthy Subjects	W2J, ZC7

Study Number/Phase	Study Title	Models
CXA-PEDS-13-08/ Phase 1	A Phase I, Non-comparative, Open-label Study to Characterize the Pharmacokinetics of a Single Intravenous Dose of Ceftolozane/Tazobactam in Pediatric Patients Receiving Standard of Care Antibiotic Therapy for Proven or Suspected Gram-negative Infection or for Peri-operative Prophylaxis	W2J, ZC7
MK-7625A-007 (CXA-ICU-14-01)/ Phase 1	A Phase 1, Prospective, Multicenter, Open- label Study to Assess the Plasma Pharmacokinetics and Lung Penetration of Intravenous (IV) Ceftolozane/Tazobactam in Critically Ill Patients	W2J, ZC7
MK-7625A-013/ Phase 3	A Multicenter, Open-label, Noncomparative, Japanese Phase 3 Study to Assess the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) used in Combination with Metronidazole in Japanese Patients with cIAI	ZC7
MK-7625A-014/ Phase 3	A Multicenter, Open-label, Noncomparative, Japanese Phase 3 Study to Assess the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) in Japanese Patients with Uncomplicated Pyelonephritis and cUTI	ZC7
MK-7625A-008 (CXA-NP-11-04)/ Phase 3	A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia	ZC7

Each model consisted of at least two compartments to describe central and peripheral PK. The models mainly differ in terms of the use of covariates to describe the effect of the disease state on PK and the use of an ELF compartment. The parameters identified for ceftolozane and tazobactam in each of the newly submitted models is shown in Table 64, Table 65, Table 66, and Table 67.

Parameter Estimates

Table 64. Parameter Estimates from POP PK Model W2J: Ceftolozane.

	Final Parameter Estimate		Interindividual Variability / Residual Variability	
Parameter	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	5.65	1.41	34.7 %CV	15.3
CL: Body Weight on CL (Power)	0.786	3.54		
CL: MDRD eGFR on CL (Power)	0.676	8.31		
CL: cIAI on CL (Proportional)	1.22	6.73		
CL: Pneumonia on CL (Proportional)	0.724	10.3		
V_c: Volume of Distribution for Central Compartment (L)	9.94	2.28	41.3 %CV	28.3
V_c: Body Weight on V_c (Power)	1.17	5.73		
V_c: cIAI on V_c (Proportional)	1.42	10.9		
V_c: Pneumonia on V_c (Proportional)	1.78	6.37		
V_c: Other Infection on V_c (Proportional)	1.43	9.32		
Q: Intercompartmental Clearance (L/h)	2.60[a]	9.81	NE	NA
V_p: Volume of Distribution for Peripheral Compartment (L)	4.32[a]	4.23	16.2 %CV	41.8
V_p: Body Weight on V_p (Power)	0.593	6.23		
K_{1E}: Rate Constant for Disposition From Plasma to ELF (1/h)	0.808	11.6	39.6 %CV for healthy subjects	28.1 for healthy subjects
			81.2 %CV for patients with pneumonia	46.0 for patients with pneumonia
K_{E0}: Rate Constant for Elimination From ELF (1/h)	1.56	8.97	NE	NA
Pneumonia on K_{1E} and K_{E0} (Proportional)	0.0339	44.0	NA	NA
cov(IIV in V_c, IIV in CL)	0.0597[b]	29.2	NA	NA
RV Proportional	0.0249	12.7	92.7 - 15.8 %CV[c] F [0.1 - 100]	NA
RV Additive	0.00834	21.4		
Minimum Value of the Objective Function = 20934.225				

Abbreviations: cIAI, complicated intra-abdominal infection; %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; ELF, epithelial lining fluid; IIV, interindividual variability; MDRD, modification of diet in renal disease; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; RV, residual variability.

[a] The following parameter estimates were found to be highly correlated ($r^2 \geq 0.810$): V_p: volume of distribution for peripheral compartment (L),Q: Intercompartmental clearance (L/h).

[b] The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.173 for cov(IIV in V_c, IIV in CL).

[c] The residual variability (%CV) was calculated using the following equation: (SQRT(power(F,2) × 0.0249 + 0.00834)/F) × 100.

Table 65. Parameter Estimates from POP PK Model W2J: Tazobactam.

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	20.6	2.29	50.4 %CV	21.2
CL: Body Weight on CL (Power)	0.863	5.30		
CL: MDRD eGFR on CL (Power)	0.606	12.7		
CL: cIAI on CL (Proportional)	0.646	8.99		
CL: Pneumonia on CL (Proportional)	0.590	13.2		
V_c: Volume of Distribution for Central Compartment (L)	13.2	2.85	45.4 %CV	37.2
V_c: Body Weight on V_c (Power)	0.933	6.82		
V_c: Pneumonia on V_c (Proportional)	1.85	7.12		
V_c: Other Infection on V_c (Proportional)	1.59	13.5		
Q: Intercompartmental Clearance (L/h)	3.90	5.20	NE	NA
Q: Body Weight on Q (Power)	0.750	FIXED		
V_p: Volume of Distribution for Peripheral Compartment (L)	4.79	3.18	28.4 %CV	36.0
V_p: Body Weight on V_p (Power)	0.832	5.68		
V_p: cIAI on V_p (Proportional)	1.19	11.5		
V_p: Pneumonia on V_p (Proportional)	2.72	19.3		
K_{1E}: Rate Constant for Disposition From Plasma to ELF (1/h)	0.262[a]	30.6	65.5 %CV for healthy subjects	23.9 for healthy subjects
			84.4 %CV for patients with pneumonia	34.5 for patients with pneumonia
K_{E0}: Rate Constant for Elimination From ELF (1/h)	0.691[a]	25.1	NE	NA
Pneumonia on K_{1E} and K_{E0} (Proportional)	0.479	44.0	NA	NA
cov(IIV in V_c, IIV in CL)	0.129[b]	41.6	NA	NA
RV Proportional	0.0549	12.3	23.4 %CV	NA
Minimum Value of the Objective Function = 5258.166				

Abbreviations: cIAI, complicated intra-abdominal infection; %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; ELF, epithelial lining fluid; IIV, interindividual variability; MDRD, modification of diet in renal disease; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; RV, residual variability.

[a] The following parameter estimates were found to be highly correlated ($r^2 \geq 0.810$): K_{E0}: rate constant for elimination from ELF (1/h), K_{1E}: rate constant for disposition from plasma to ELF (1/h).

[b] The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.318 for cov(IIV in V_c, IIV in CL).

Of note, the rate constant for disposition from plasma to ELF in pneumonia patients (product of K1E and the pneumonia factor) is significantly lower for TOL (0.0274 hr^{-1}) than for TAZ (0.125 hr^{-1}), which translates to an ELF distribution half-life of approximately 26 hr and 6 hr, respectively. However, it is possible that this rate constant was not characterized well because all ELF PK samples were collected on the last day of therapy 1-8 hours following the final dose. Instead,

this longer ELF distribution half-life of TOL appears to may be influenced by two outliers 30-40 hr after the start of therapy. Thus, the model may not be able to accurately predict ELF concentrations on Day 1 of therapy.

Table 66. Parameter Estimates from POP PK Model ZC7: Ceftolozane.

	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
Parameter	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	4.84	1.66	36.1 %CV	8.19
CL: Exponent of (CrCL/100) for CL	0.701	4.32		
CL: Fold-Change in CL for cUTI	1.18	2.99		
CL: Fold-Change in CL for cIAI	1.43	2.99		
CL: Fold-change in CL for ESRD	0.320	10.9		
V_c: Volume of Distribution of the Central Compartment (L)	9.23	1.83	42.9 %CV	16.5
V_c: Fold-Change in V_c for cUTI	1.25	3.52		
V_c: Fold-Change in V_c for cIAI	1.59	4.97		
V_c: Fold-Change in V_c for Pneumonia	2.00	3.29		
V_c: Fold-Change in V_c for Other Infections	2.14	14.8		
V_c: Exponent of (WTKG/70) for V_c	0.684	9.69		
V_c: Fold-change in V_c for ESRD	1.30	11.7		
Q: Intercompartmental Clearance (L/h)	3.13[b]	6.93	NE	NA
V_p: Volume of Distribution of the Peripheral Compartment (L)	4.78[b]	3.24	15.1 %CV	57.8
V_p: Exponent of (WTKG/70) for V_p	0.484	16.3		
cov(IIV in V_c, IIV in CL)[c]	0.0733	17.1	NA	NA
Residual Variability Proportional	0.0248	7.20	15.7 %CV[d]	NA
Residual Variability Additive	0.00984	17.8	0.0992 SD[d]	NA
Minimum Value of the Objective Function = 32902.322				

Abbreviations: cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation expressed as a percent; ESRD, end-stage renal disease; IIV, interindividual variability; NA, not applicable; NE, not estimated; OINF, other infection types; %RSE, relative standard error expressed as a percent; SD, standard deviation (µg/mL); V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; WTKG, body weight (kg).

[a] Eta shrinkage: eta_CL: 1.76%, eta_V_c: 9.27%, eta_V_p: 55.8%.

[b] The following parameter estimates were found to be highly correlated ($r \geq 0.924$): (V_p: volume of distribution of the peripheral compartment (L), Q: intercompartmental clearance (L/h)).

[c] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.474 for cov(IIV in V_c, IIV in CL).

[d] The magnitude of residual variability ranged from 100 %CV to 15.7 %CV over the range of 0.1 to 200 µg/mL in individual predicted ceftolozane concentrations.

Note: Other infections includes critically ill adult patients from Group 2 in Study MK-7625A-007.

Table 67. Parameter Estimates from POP PK Model ZC7: Tazobactam

Parameter	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
	Typical Value	%RSE	Magnitude	%RSE
CL: Systemic Clearance (L/h)	16.6	1.80	53.1 %CV	11.0
CL: Exponent of (CrCL/100) for CL	0.623	6.42		
CL: Fold-Change in CL for ESRD	0.626	14.6		
V_c: Volume of Distribution of the Central Compartment (L)	13.1	1.96	38.7 %CV	19.1
V_c: Fold-Change in V_c for cIAI	1.49	3.70		
V_c: Fold-Change in V_c for Pneumonia	2.17	4.46		
V_c: Fold-Change in V_c for Other Infections	2.49	16.5		
V_c: Exponent of (WTKG/70) for V_c	0.629	10.7		
V_c: Fold-Change in V_c for ESRD	0.749	11.0		
Q: Intercompartmental Clearance (L/h)	4.05	3.81	NE	NA
V_p: Volume of Distribution of the Peripheral Compartment (L)	4.89	2.59	19.4 %CV	54.7
V_p: Fold-Change in V_p for cUTI	1.25	4.27		
V_p: Fold-Change in V_p for cIAI	1.34	4.57		
V_p: Fold-Change in V_p for Pneumonia	2.06	8.89		
V_p: Exponent of (WTKG/70) for V_p	0.530	14.4		
cov(IIV in V_c, IIV in CL)[b]	0.0705	33.3	NA	NA
Residual Variability Proportional	0.0813	7.09	28.5 %CV	NA
Minimum Value of the Objective Function = 11256.828				

Abbreviations: cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation expressed as a percent; ESRD, end-stage renal disease; IIV, interindividual variability; NA, not applicable; NE, not estimated; OINF, other infection types; %RSE, relative standard error expressed as a percent; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; WTKG, body weight (kg).

[a] Eta shrinkage: eta_CL: 2.23%, eta_V_c: 23.2%, eta_V_p: 34.7%.

[b] The calculated correlation coefficient (r) of the off-diagonal omegas was 0.344 for cov(IIV in V_c, IIV in CL).

Note: Other infections includes critically ill adult patients from Study MK-7625A-007.

Of note, ESRD was used as a covariate on central volume (Vc) and clearance (CL) for both TOL and TAZ. The presence of ESRD results in a lower CL for both TOL and TAZ relative to subjects without ESRD after the differences in creatinine clearance are accounted for. This may suggest that creatinine clearance is not fully descriptive of the changes in clearance due to changes in renal function. Alternately, the exponent-based covariate structure may be incorrect for these models, particularly considering that high values of creatinine clearance were not censored.

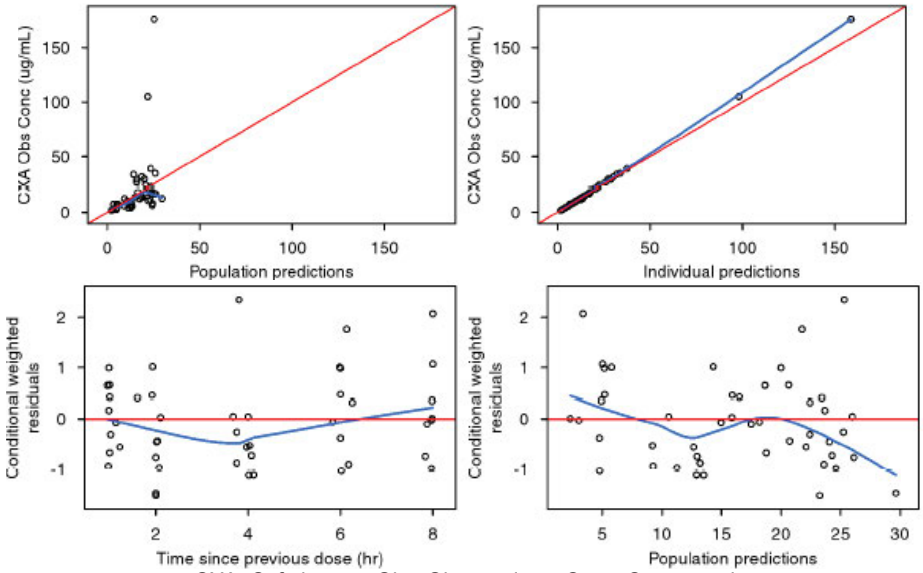
On the other hand, the presence of ESRD results in an approximately 30% higher Vc for TOL and a 25% lower Vc for TAZ relative to subjects without ESRD. These covariate relationships were not found to be statistically significant during covariate selection with p-values of approximately 0.10-0.15, which did not meet the predefined cutoff criteria. Instead, these covariate relationships were incorporated into the model based on improvement of goodness of fit and residual plots. Additionally, the trend in the effect of ESRD on Vc appears to be inconsistent between TOL and TAZ. Because PK samples were collected from only six patients with ESRD, it is plausible to include covariates without meeting a prespecified statistical significance threshold. It is not clear if this change in Vc is physiologically plausible (especially because it is inconsistent between TOL and TAZ); however, it may not have a significant effect

on the overall outcome of the analysis due to a small magnitude of the change in Vc (≤ 30%) due to ESRD.

Goodness of Fit

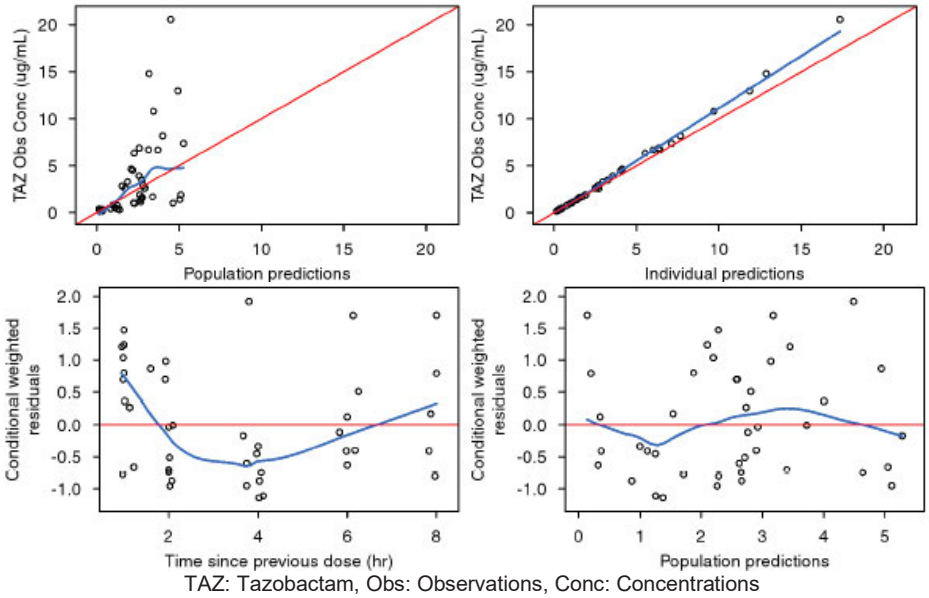
The goodness-of-fit (GOF) plots for TOL and TAZ ELF PK data (Model W2J) displayed in Figure 4 and Figure 5, respectively, show reasonable agreement between the observations and the predictions. However, given that there was only one ELF sample per patient, the IPRED (individual prediction) vs. observation panels may be misleading because the values of inter-individual variability (ETA) would explain the entire deviation from the prediction. Additionally, there appear to be trends for under-prediction around 4 hours after the previous dose and at high values of the population prediction based on the conditional weighted residuals (CWRES), which may be indicative of slight model misspecification.

Figure 4. GOF Plots for ELF PK Data in Model W2J: Ceftolozane



CXA: Ceftolozane, Obs: Observations, Conc: Concentrations

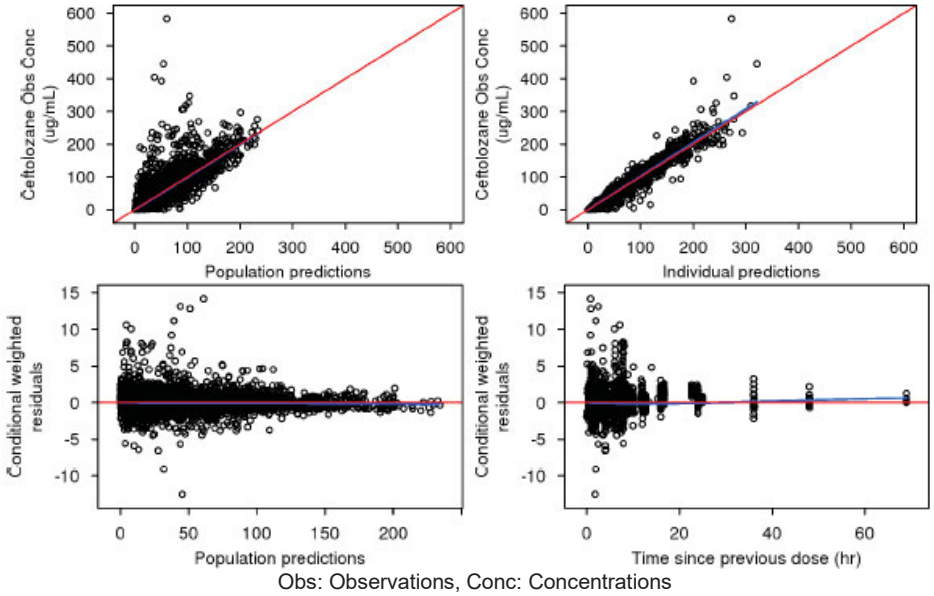
Figure 5. GOF Plots for ELF PK Data in Model W2J: Tazobactam.



TAZ: Tazobactam, Obs: Observations, Conc: Concentrations

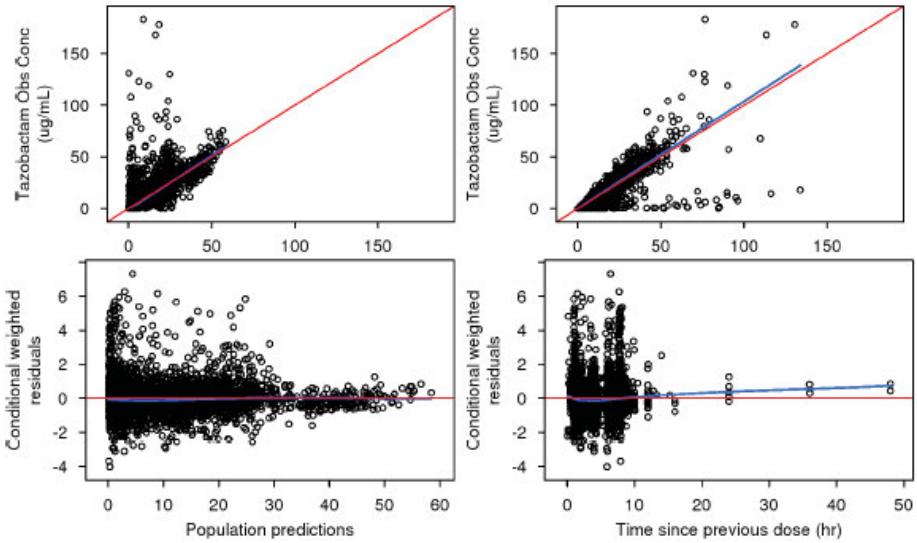
The GOF plots for TOL and TAZ plasma PK (Model ZC7) as shown in Figure 6 and Figure 7, respectively, show reasonable agreement between the observations and the predictions. Additionally, the CWRES appear to be reasonably well distributed, with a tendency towards lower variability at the high extremity of population predictions and time after the previous dose. This may be because limited subjects received a higher dose TOL/TAZ and had PK samples collected through 48 hours after their last dose.

Figure 6. GOF Plots for Plasma PK Data in Model ZC7: Ceftolozane



Obs: Observations, Conc: Concentrations

Figure 7. GOF Plots for Plasma PK Data in Model ZC7: Tazobactam



Obs: Observations, Conc: Concentrations

For simulation, the models were combined to estimate the combination of disease, ESRD, and HD-related effects on PK. Although the parameters from each model were never estimated in one single unified model, we consider this approach to be adequate for the purpose of simulation based on the goodness of fit of each model and similarity of the parameters identified in each model.

Probability of Target Attainment Analysis

This section of the review on the probability of target attainment analysis focuses on HABP/VABP patients with ESRD. The proposed doses in HABP/VABP patients with other renal function are exactly doubled from the corresponding doses in cIAI and cUTI patients. This doubling of the dose in HABP/VABP patients is supported by the finding of efficacy of cIAI and cUTI at the target exposure in the previous submission of this NDA along with the finding of an approximate 50-60% penetration of TOL and TAZ from plasma into ELF as described further in Section 6 of this multidisciplinary review. On the other hand, the proposed dose in HABP/VABP patients with ESRD is tripled from the corresponding dose in cIAI and cUTI patients and, therefore, further review is needed to evaluate the proposed dose using the target attainment analysis.

The model for simulation was developed by combining the PK parameters from three different PK models. The final simulation model included the effects of infection and ESRD on plasma PK (ZC7), the effect of hemodialysis on PK (POPPK-002), and the relationship between ELF and plasma concentrations (W2J). All other structural parameters and variability terms were drawn from Model ZC7 as it was generated from the most data, allowing for the most robust analysis.

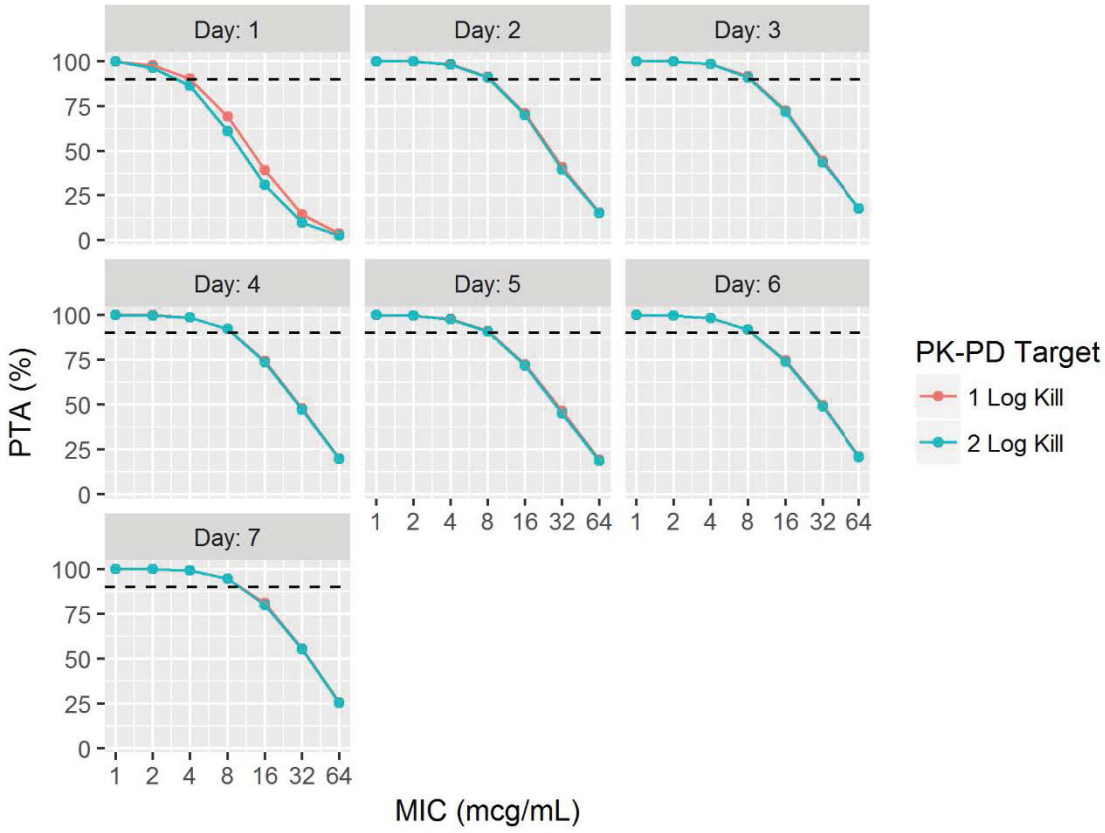
A dataset for simulation of approximately 1000 virtual patients was generated using the Applicant's covariate distribution of age and weight and creatinine clearance. The simulation

was performed at the proposed dose of TOL/TAZ in patients with ESRD: a single loading dose of TOL/TAZ 2.25 g (1.5 g TOL and 0.75 g TAZ) followed by a maintenance dose of TOL/TAZ 0.45 g (0.3 g TOL and 0.15 g TAZ) intravenous every 8 hours. Each patient was simulated to receive doses of TOL/TAZ for a total duration of 7 days. Concentrations of TOL and TAZ in ELF were used to conduct the PTA analysis.

There was one significant change in this reviewer's analysis compared to the Applicant's analysis. The Applicant assumed that the true ELF-related inter-individual variability (IIV) as measured by the coefficient of variation (CV%) is half of the IIV CV% identified empirically in Model W2J due to the low sample size of patients with pneumonia who received TOL and TAZ and had ELF concentrations collection from them. However, this reviewer found the Applicant's assumption to be inadequate and performed the simulation and PTA analysis using the original IIV estimated in Model W2J.

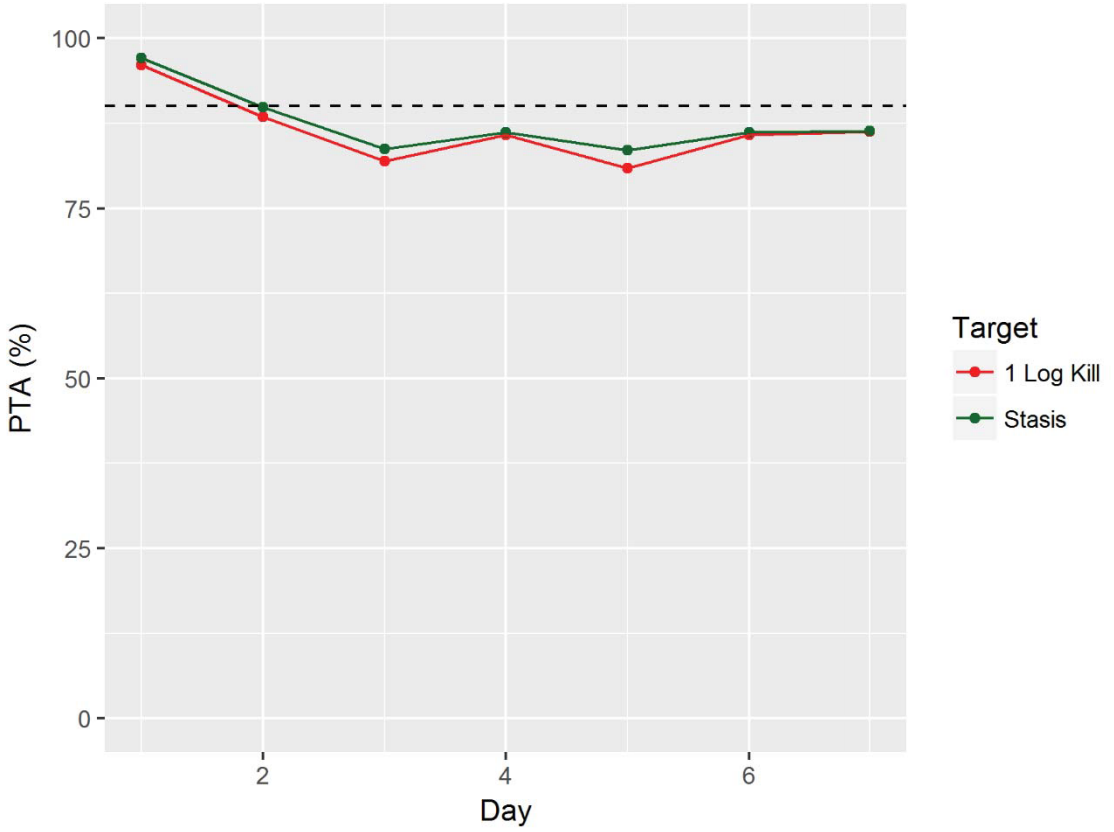
Additionally, although the PK models were determined by the review team to be inadequate to describe ELF PK on Day 1, the PTA estimates were still considered appropriate and are included in the subsequent analysis. The PTA of TOL and TAZ at the proposed dose in patients with ESRD stratified by day is shown in Figure 8 and Figure 9.

Figure 8. PTA of Ceftolozane by Day at the Proposed Dose in Simulated Patients With ESRD Using Model W2J With Original Variability



The dashed lines represent 90% PTA.

Figure 9. PTA of Tazobactam by Day at the Proposed Dose in Simulated Patients with ESRD Using Model W2J With Original Variability



The horizontal dashed line represents 90% PTA.

Table 68 shows the highest theoretical MIC (TOL) that 90% of the simulated population could achieve after administration of the proposed dose. Essentially, this table demonstrates at what MIC the PTA attainment reaches and becomes lower than 90% (as represented by the horizontal dashed lines in Figure 8). This table also demonstrates the difference between the Applicant's version of the analysis where the ELF IIV CV% was halved compared to the simulation conducted by the reviewer, which uses the original ELF PK variability as reported in Model W2J.

Table 68. Highest Theoretical MIC (Ceftolozane, mcg/mL) for Which 90% of Simulated Patients Would Achieve the Designated PK-PD Target When Administered the Proposed Dose of TOL/TAZ by Day

	Ceftolozane			
	Reduced Variability (Submitted by Applicant)		Original Variability (in Model W2J)	
Day	1 Log Kill	2 Log Kill	1 Log Kill	2 Log Kill
1	6.51	5.41	4.04	3.36
2	14.3	13.7	8.61	8.29
3	14.8	14.2	8.59	8.42
4	15.4	15.1	9.15	8.94
5	13.7	13.3	8.45	8.27
6	14.9	14.5	9.09	8.91
7	18.6	18.1	10.8	10.6

For the TOL PTA calculated using the model with reduced variability as submitted by the Applicant, 90% of patients are uniformly able to achieve the PK-PD targets at higher TOL MICs relative to the TOL PTA calculated using the model with the original variability in Model W2J. Additionally, these patients achieve the targeted MIC (4 mcg/mL TOL) throughout the course of treatment. Greater than 90% of patients achieve the PK-PD target for TAZ as well in the PTA analysis using the model with reduced variability. However, the rationale for the assumption that the actual ELF PK IIV is lower than what was identified empirically is inadequate to rely on this PTA alone as discussed previously.

For TOL PTA calculated using the model with original variability, 90% of patients achieve the PK-PD target for 1 log kill at an MIC of 4 mcg/mL throughout the duration of the trial. Patients are able to achieve the TOL PK-PD target at higher MICs with increasing day, largely due to the low intercompartmental (plasma-ELF) clearance of TOL, which necessitates a few days to reach steady state concentrations in the ELF. The MICs reached with the TOL PK-PD target for 2-log kill is lower than that of 1-log kill but comparable, indicating no meaningful difference between the use of 1 log kill and 2-log kill as a PK-PD target in the ESRD population. There are also lower PTAs on Days 3 and 5 on which HD is administered relative to other days.

For TAZ PTA calculated using the model with original variability, 90% of patients achieve the PK-PD target for stasis at a threshold concentration of 1 mcg/mL on Days 1 and 2. PTA is lower starting on Day 3 when HD is administered; at this time, the probability of the PK/PD target were 80-90%. Because the TOL PTA analysis demonstrated that TOL can achieve the PK-PD target for MICs far above its target MIC (4 mcg/mL), the high TOL PTA will likely compensate for slightly lower TAZ PTA.

The difference between TAZ and TOL appears to be caused by the effects of ESRD and HD. TAZ PTA is more affected by HD than TOL PTA because TOL has a relatively lower total clearance and inter-compartmental clearance in patients with HABP/VABP and ESRD. Thus, TAZ ELF exposure equilibrates with the plasma exposure more rapidly and is more responsive to changes caused by HD. On the other hand, there does not appear to be a meaningful difference

between the use of the two different PK-PD targets (in this case, stasis and 1 log kill) to evaluate the PTA of TAZ as was also true for TOL.

In order to evaluate an alternate scenario, this PTA approach was used to assess the target attainment if the dose administered to patients with HABP/VABP and ESRD was twice the dose administered to patients with cIAI/cUTI and ESRD (2x dose) instead of three times the dose. Table 69 shows the highest theoretical MIC (TOL) that 90% of the simulated population could achieve after administration of 2x dose. TOL ELF concentrations are sufficient to achieve the PK-PD target for an MIC of 4 mcg/mL on Days 2-7 in over 90% of patients. On the other hand, TAZ ELF concentrations only achieve the PK-PD target in 70-80% of patients. Altogether, the results demonstrate that the 2x dose would not be sufficient.

Table 69. Highest Theoretical MIC (Ceftolozane, mcg/mL) for Which 90% of Simulated Patients Would Achieve the Designated PK-PD Target When Administered the 2x Dose of TOL/TAZ by Day

	Ceftolozane	
Day	**1 Log Kill**	**2 Log Kill**
1	2.87	2.37
2	6.30	6.04
3	6.35	6.22
4	6.73	6.57
5	6.24	6.11
6	6.82	6.63
7	8.44	8.24

Overall, the PTA analysis supports the need for a three-fold higher dose in HABP/VABP patients with ESRD relative to cUTI and cIAI patients with ESRD.

15.5. Additional Clinical Safety Tables

Table 70. Subjects with AEs With Fatal Outcomes by Country, Demographics, Study Day of Death and Exposure Duration and Study Day of Last Dose

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
Ceftolozane/tazobactam							
(b) (6)	BEL	64, M, W	Haemorrhage intracranial	(b) (6)	7.1	(b) (6)	8
	BEL	61, M, W	Respiratory failure		7.7		9
	BEL	84, M, W	Acute respiratory distress syndrome		4.5		6
	BRA	61, F, O	Neurological decompensation		9.7		11
	BRA	62, M, O	Acute respiratory failure		12.4		14
	BRA	65, F, W	Multi-organ failure		9.7		11
	BRA	76, M, W	Septic shock		9.7		11
	BRA	54, M, W	Septic shock		2.4		4
	BRA	59, M, B or AfAm	Brain death		4.1		5
	BRA	66, F, W	Brain death		9.7		11
	HRV	79, F, W	Multi-organ failure		7.7		9
	HRV	79, M, W	Death		0.7		2
	CZE	72, M, W	Cerebral haemorrhage		5.1		7
	CZE	81, M, W	Septic shock		2		3
	CZE	64, F, W	Septic shock		13.7		15
	CZE	69, F, W	Cerebral haemorrhage		7.7		9
	CZE	80, M, W	Septic shock		7.7		9
	CZE	62, F, W	Septic shock		1.5		3
	CZE	66, F, W	Brain death		8.7		10
	CZE	76, M, W	Cardiac failure		7.7		9
	CZE	84, M, W	Chronic respiratory failure		7.7		9
	EST	54, M, W	Cerebral haemorrhage		7.6		9

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	EST	50, M, W	Pulmonary embolism	(b) (6)	7.7	(b) (6)	9
	EST	47, M, W	Sepsis		8.7		10
	FRA	67, M, NR	Haemorrhagic stroke		7.7		9
	FRA	70, F, W	Gastrointestinal ischaemia		7.7		9
	FRA	81, M, NR	Respiratory failure		5.7		7
	FRA	64, F, NR	Mental impairment		1.4		3
	FRA	77, M, NR	Multi-organ failure		1.3		3
	FRA	50, F, NR	Acute pulmonary oedema		6.7		8
	DEU	71, M, W	Systemic inflammatory response syndrome		7		8
	GTM	24, M, W	Cardio-respiratory arrest		3.		5
	HUN	40, M, W	Cardiac failure		4.7		6
	ISR	88, F, W	Septic shock		3.4		4
	KOR	77, F, A	Pneumonia		1.7		3
	PHL	54, M, A	Neurogenic shock		7.8		9
	PHL	82, M, A	Cardiac failure		7.7		9
	PHL	38, M, A	Brain herniation		13.5		15
	PHL	68, M, A	Sepsis		6.2		7
	PHL	84, F, A	Septic shock		7.6		9
	PHL	79, M, A	Hypovolaemic shock		7.7		9
	PHL	79, M, A	Upper gastrointestinal haemorrhage		7.7		9
	PHL	52, M, A	Pneumonia aspiration		13.7		14
	PHL	67, M, A	Brain herniation		1.7		3
	RUS	56, M, W	Intraventricular haemorrhage		1.		3
	RUS	85, M, W	Death		7		8

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	RUS	80, F, W	Death	(b) (6)	10.7	(b) (6)	12
	RUS	70, F, W	Multi-organ failure		7.7		9
	RUS	69, M, W	Cardiac failure acute		13.7		15
	RUS	86, M, W	Cardiac failure acute		10.4		11
	RUS	82, M, W	Cardiac failure acute		7.7		9
	RUS	44, M, W	Brain oedema		0.7		2
	RUS	47, F, W	Brain oedema		8.7		10
	RUS	68, M, W	Sepsis		8.7		10
	RUS	81, F, W	Multi-organ failure		1.7		3
	RUS	71, F, W	Multi-organ failure		7.7		9
	RUS	84, M, W	Brain midline shift		2.4		4
	RUS	67, M, W	Lung abscess		3.7		5
	RUS	65, M, W	Pulmonary embolism		7.7		9
	RUS	57, F, W	Multi-organ failure		5.6		7
	RUS	59, M, W	Multi-organ failure		0.7		2
	RUS	86, F, W	Brain oedema		13.4		15
	RUS	59, M, W	Multi-organ failure		5.7		7
	RUS	88, F, W	Pulmonary embolism		6.		8
	RUS	64, M, W	Brain oedema		2		3
	RUS	67, F, W	Pulmonary embolism		7.7		9
	RUS	56, M, W	Brain midline shift		4.8		6
	RUS	61, M, W	Multi-organ failure		13.4		14
	RUS	89, F, W	Acute myocardial infarction		12.4		14
	RUS	66, F, W	Multi-organ failure		13.7		15
	RUS	53, M, W	Cardiac failure		9.7		11

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	RUS	32, M, W	Metabolic acidosis	(b) (6)	1	(b) (6)	2
	RUS	71, F, W	Multi-organ failure		1.7		3
	SRB	63, M, W	Respiratory failure		9.5		10
	SRB	65, M, W	Hypovolaemic shock		7.7		9
	SRB	57, F, W	Cardiac arrest		9.4		11
	SRB	77, M, W	Pneumonia		7.7		9
	ZAF	30, M, B or AfAm	Brain herniation		0.3		1
	ESP	54, F, W	Respiratory failure		8.7		10
	ESP	75, M, W	Respiratory failure		11.9		13
	UKR	36, M, W	Brain oedema		13.4		14
	UKR	58, F, W	Cardiac failure acute		3.7		5
	UKR	79, M, W	Multi-organ failure		6		7
	UKR	72, M, W	Brain midline shift		8.1		9
	UKR	78, M, W	Brain midline shift		13.7		15
	UKR	79, M, W	Cardiac failure acute		2.4		4
	UKR	78, F, W	Acute myocardial infarction		4.4		6
	UKR	44, M, W	Brain oedema		0.8		2
	UKR	75, M, W	Brain oedema		3		4
	UKR	45, M, W	Haemorrhagic stroke		4.4		6
	UKR	58, M, W	Brain injury		7.7		9
	UKR	68, M, W	Haemorrhagic stroke		13.7		15
	USA	82, M, W	Multi-organ failure		2.2		4
	USA	54, F, W	Cerebral haemorrhage		7.3		9
	USA	50, M, W	Respiratory failure		0.7		2
	USA	75, M, W	Cerebral haemorrhage		2.7		4

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	GEO	89, M, W	Cardiovascular insufficiency	(b) (6)	13.8	(b) (6)	15
	GEO	50, F, W	Brain oedema		5.7		7
	GEO	58, M, W	Cardiac arrest		1.4		3
	GEO	87, M, W	Cardiovascular insufficiency		1.7		3
	GEO	90, M, W	Cardiac arrest		8		9
	GEO	64, M, W	Cardiac failure acute		4.		6
	GEO	78, F, W	Cardiac failure acute		2.		4
	GEO	67, F, W	Cardiac failure acute		7.7		9
	GEO	77, M, W	Cardiac failure		7.7		9
	GEO	79, F, W	Cardiac failure		7.7		9
	GEO	60, M, W	Cardiac failure acute		7.7		9
Meropenem arm							
(b) (6)	AUS	63, M, W	Brain injury	(b) (6)	4.4	(b) (6)	6
	AUS	74, M, W	Pulseless electrical activity		13.7		15
	BEL	77, M, W	Respiratory failure		1.7		3
	BEL	66, F, W	Cerebral ischaemia		3.6		5
	BRA	62, M, W	Sepsis		8.7		10
	BRA	55, M, B or AfAm	Brain oedema		7.7		9
	BRA	67, F, W	Arrhythmia		12.7		14
	BRA	68, M, W	Multi-organ failure		0.6		2
	BRA	74, F, W	Acute respiratory failure		1.7		3
	COL	72, M, AI or AN	Cardio-respiratory arrest		5.4		7
	HRV	73, M, W	Death		13.7		15
	HRV	75, M, W	Death		7.7		9
	HRV	86, F, W	Death		11.4		12

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	CZE	58, F, W	Pneumonia	(b) (6)	13.7	(b) (6)	15
	CZE	68, M, W	Septic shock		7.7		9
	CZE	70, F, W	Septic shock		7.7		9
	CZE	56, F, W	Septic shock		13.7		15
	CZE	71, M, W	Septic shock		6.4		7
	CZE	75, M, W	Cardiac failure		7.7		9
	CZE	85, M, W	Shock haemorrhagic		7.7		9
	CZE	60, M, W	Wernicke's encephalopathy		7.7		9
	CZE	82, M, W	Cardiac failure		7.7		9
	CZE	69, M, W	Cardiac failure		7.7		9
	CZE	74, F, W	Cardiac arrest		7.7		9
	CZE	80, M, W	Multi-organ failure		7.7		9
	CZE	77, M, W	Bronchopneumonia		3.4		5
	CZE	61, M, W	Ischaemic stroke		7.7		9
	EST	62, M, W	Cardiac failure acute		0.		1
	FRA	66, M, NR	Pneumonia		7.7		9
	FRA	60, M, NR	Apallic syndrome		9.3		11
	FRA	62, M, NR	Brain death		0.4		1
	FRA	56, M, NR	Septic shock		3.7		5
	FRA	67, M, NR	Septic shock		5.7		7
	FRA	74, F -	Acute respiratory distress syndrome		13.5		15
	FRA	69, M, NR	Malignant peritoneal neoplasm		7.7		9
	DEU	81, M, W	Multi-organ failure		7.7		9
	GTM	81, M, O	Cardio-respiratory arrest		7.7		9
	GTM	61, F, O	Hypovolaemic shock		13.6		14

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	HUN	72, F, W	Respiratory distress	(b) (6)	0.7	(b) (6)	2
	ISR	79, F, W	Septic shock		7.6		9
	PHL	72, F, A	Cardio-respiratory arrest		7.8		9
			Chronic obstructive pulmonary disease		7.8		9
			Multi-organ failure		7.8		9
	PHL	61, M, A	Septic shock		0.5		2
	PHL	55, M, A	Acute respiratory failure		4.5		6
	PHL	75, M, A	Renal failure acute		7.9		8
	PHL	75, M, A	Multi-organ failure		7.9		8
	RUS	59, M, W	Death		0.4		2
	RUS	60, M, W	Cerebrovascular accident				4
	RUS	74, M, W	Pulmonary embolism		11.7		13
	RUS	73, F, W	Cerebellar haemorrhage		7.6		9
	RUS	69, M, W	Myocardial ischaemia		0.		2
	RUS	81, M, W	Cardiogenic shock		9		10
	RUS	81, M, W	Myocardial infarction		9		10
	RUS	77, F, W	Cardiac failure acute		7.7		9
	RUS	87, F, W	Multi-organ failure		5.7		7
	RUS	41, F, W	Brain oedema		4		5
	RUS	54, M, W	Pulmonary embolism		7.7		9
	RUS	54, F, W	Brain oedema		3.4		5
	RUS	65, M, W	Acute myocardial infarction				4
	RUS	88, M, W	Multi-organ failure		7.7		9
	RUS	79, F, W	Pulmonary embolism		7.7		9
	RUS	52, M, W	Brain oedema		2		3
	RUS	69, M, W	Cardiopulmonary failure		0.		2
	RUS	61, F, W	Cardiac failure acute		7.7		9

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	RUS	31, M, W	Brain herniation	(b) (6)	6.3	(b) (6)	7
	RUS	66, F, W	Amyotrophic lateral sclerosis		13.7		15
	RUS	54, M, W	Pulmonary embolism		7.7		9
	RUS	51, F, W	Multi-organ failure		1.7		3
	RUS	56, M, W	Encephalitis		11		12
	RUS	43, M, W	Brain oedema		8.7		10
	RUS	60, M, W	Brain oedema		13.7		15
	RUS	79, F, W	Brain midline shift		5.7		7
	RUS	39, M, W	Multi-organ failure		7		8
	RUS	61, M, W	Acute myocardial infarction		0.		2
	RUS	87, F, W	Gastrointestinal haemorrhage		8.4		10
	RUS	82, M, W	Sepsis		2.1		3
	RUS	61, M, W	Respiratory failure		0.4		2
	RUS	61, M, W	Cardiac failure acute		12.4		14
	RUS	69, M, W	Endotoxaemia		7.7		9
	SRB	63, M, W	Device related sepsis		1.7		3
	SRB	70, M, W	Acute coronary syndrome		7		8
	ESP	57, F, W	Respiratory failure		6.1		7
	UKR	36, F, W	Spinal cord oedema		0.7		2
	UKR	56, F, W	Cardiac failure acute		2.		4
	UKR	92, F, W	Cardiovascular insufficiency		13.7		15
	UKR	79, F, W	Brain oedema		5.7		7
	UKR	71, F, W	Respiratory arrest		13.7		15
	UKR	60, M, W	Gastrointestinal haemorrhage		13.7		15
	UKR	42, M, W	Haemorrhagic stroke		4.		5

Unique Subject Identifier	Country	Age/Sex/ Race_	Fatal Outcome Preferred Term	Derived Death Study Day	Overall Duration Exposure (Days)	Death Days Since LD	Day of Last Exposure
(b) (6)	USA	89, F, W	Pneumonia bacterial	(b) (6)	2.4	(b) (6)	3
	USA	78, M, W	Failure to thrive		7.7		9
	USA	78, M, W	Peritonitis		11.9		13
	GEO	77, F, W	Cardiovascular insufficiency		13.8		15
	GEO	59, M, W	Brain oedema		7.7		9
	GEO	90, F, W	Cardiac death		13.7		15
	GEO	60, M, W	Septic shock		0.5		2
	GEO	88, F, W	Hypovolaemic shock		7.7		9
	GEO	72, F, W	Cardiovascular insufficiency		7.7		9
	GEO	65, M, W	Respiratory failure		2.7		4
	GEO	78, M, W	Gangrene		7.7		9
	GEO	83, M, W	Cardiac failure acute		7.7		9
	GEO	29, M, W	Cardiac arrest		0		1
	JPN	76, M, A	Upper gastrointestinal haemorrhage		4.4		5
	JPN	70, M, A	Gastrointestinal necrosis		5.7		7

Abbreviations: A=Asian; B or Af.Am=black or African American; AI or AN=American Indian or Alaska Native; O=other; NR=not reported W=white; LD=last dose.

Table 71. Patients With Worsening or Recurrent Intracranial Hemorrhage

Unique Subject Identifier	Country	Age/ Sex/ Race	Fatal Outcome Preferred Term	Adverse Event Reported Term	Results in Death	Death Study Day	Death Days Since Last Dose	Overall Duration Exp. (Days)	Start Rel Day	End Rel Day	Day of Last Exp.	Serious Event
Ceftolozane/Tazobactam Arm												
(b) (6)	BEL	64,M, W	Haemorrhage intracranial	Worsening of intracranial hemorrhage	Y		(b) (6)	7.1	20	22	8	Y
	CZE	72, M, W	Cerebral haemorrhage	Intracerebral bleeding				5.1	6	7	7	Y
	CZE	69, F, W	Cerebral haemorrhage	Intracerebral bleeding				7.7	10	14	9	Y
	EST	54, M, W	Cerebral haemorrhage	New episode of intracerebral hemorrhage	Y			7.6	30	31	9	Y
	FRA	67, M, NR	Haemorrhagic stroke	Hemorragic stroke				7.7	12	12	9	Y
	GTM	24, M, W	Subarachnoid haemorrhage	Subarachnoid hemorrhage				3.7	4	.	5	N
	PHL	38, M, A	Brain herniation	Uncal Herniation secondary to Cerebrovascular Bleed Left Basal Ganglia and Temporo-parietal Area.	Y			13.5	22	22	15	Y
	PHL	67, M, A	Brain herniation	Uncal Herniation	Y			1.7	3	3	3	Y
	RUS	56, M, W	Intraventricular haemorrhage	Gemotamponada ventricles of the brain				1.4	5	5	3	Y

Unique Subject Identifier	Country	Age/ Sex/ Race	Fatal Outcome Preferred Term	Adverse Event Reported Term	Results in Death	Death Study Day	Death Days Since Last Dose	Overall Duration Exp. (Days)	Start Rel Day	End Rel Day	Day of Last Exp.	Serious Event
(b) (6)	RUS	25, M, W	Cerebral haematoma	Hematoma to the right frontal lobe		.	.	13.7	18	32	15	N
	ZAF	30, M, B or AfAm	Brain* herniation	Cerebral Herniation			(b) (6)	0.3	1	1	1	Y
	UKR	75, M, W	Cranio-cerebral injury	Exacerbation of the closed craniocerebral injury				3	4	.	4	N
	UKR	75, M, W	Subdural haematoma	Progression of subdural hematoma of the left hemisphere				3	4	.	4	N
	UKR	45, M, W	Haemorrhagic stroke	Outcome of index disease, hemorrhagic stroke				4.4	6	6	6	Y
	UKR	68, M, W	Haemorrhagic stroke	Progression of hemorrhage stroke	Y			13.7	36	36	15	Y
	USA	54, F, W	Cerebral haemorrhage	Intra-cerebral hemorrhage	Y			7.3	35	35	9	Y
	USA	75, M, W	Ischaemic cerebral infarction	Infarction in posterior circulation distribution				2.7	4	.	4	Y
	USA	75, M, W	Cerebral haemorrhage	Worsening subarachnoid, subdural, and intraventricular hemorrhage				2.7	4	8	4	Y

Unique Subject Identifier	Country	Age/ Sex/ Race	Fatal Outcome Preferred Term	Adverse Event Reported Term	Results in Death	Death Study Day	Death Days Since Last Dose	Overall Duration Exp. (Days)	Start Rel Day	End Rel Day	Day of Last Exp.	Serious Event
(b) (6)	IRL	59, M, W	Ischaemic cerebral infarction	Watershed infraction cerebral		.	.	13.7	7	.	15	N
	GEO	50, F, W	Cerebral haematoma	Intracerebral hematoma		(b) (6)	.	5.7	6	6	7	Y
Meropenem Arm												
(b) (6)	PHL	55, M, A	Brain* herniation	Transtentorial herniation		(b) (6)	.	4.5	10	.	6	Y
	RUS	73, F, W	Cerebellar haemorrhage	Intracerebral hemorrhage in the cerebellum with a breakthrough of blood in the IV ventricle	Y	(b) (6)		7.6	21	21	9	Y
	RUS	63, F, W	Subdural haematoma	Recurrence of subdural hematoma	N	.	.	13.8	15	15	15	Y
	RUS	31, M, W	Haemorrhage intracranial	Recurrent intracranial bleeding		(b) (6)	.	6.3	3	3	7	N
	RUS	31, M, W	Brain herniation	Coning of brain stem	Y	(b) (6)		6.3	7	7	7	Y
	UKR	49, M, W	Haemorrhagic transformation stroke	Hemorrhagic transformation of ischemic stroke extensive right hemisphere of the brain		.	.	7.6	11	.	9	N
	UKR	42, M, W	Haemorrhagic stroke	Progression of hemorrhage stroke		(b) (6)		4.4	5	5	5	Y

Abbreviations: A=Asian; B or AfAm=black or African American; NR=not reported W=white; Exp. = exposure.*: hemorrhage, although possible, was not confirmed in these 2 cases.

15.5.1. Comments Regarding Patients with Worsening Intracranial Hemorrhage

(b) (6)

55-Year-Old Asian Male, Meropenem Ventilated HABP Arm

Admission diagnosis: Acute respiratory failure. GI hemorrhage on Day 5. Completed 6 days of treatment. Had brain herniation on Day 10. No specific mention of intracranial hemorrhage or alternative cause of brain herniation.

(b) (6)

73-Year-Old White Female, Meropenem VABP Arm

"Cerebral hemorrhage on admission Day -12. Thrombocytopenia Days 3-4. Completed 9 days of treatment. Intracerebral hemorrhage in the cerebellum with a breakthrough of blood in the IV ventricle. Day 21 cerebellar hemorrhage. Heparin prophylaxis."

(b) (6)

63-Year-Old White Female, Meropenem VABP Arm

"Day -20 craniocerebral injury. Day (b) (6) admitted with ischemic stroke, subdural hematoma. Recurrence of subdural hematoma on Day 15. Last dose of treatment on Day 15. Test of cure on Day 24, 'cure.' Subdural hematoma, ENOXAPARIN prophylaxis. Liquorrhea. Cerebrospinal fluid leakage."

(b) (6)

31-Year-Old White Male, Meropenem VABP Arm

"Cerebellar hemorrhage on admission on Day -9. Completed 7 days of treatment. Recurrent intracranial bleeding. Hemorrhage intracranial Day 7. Coning of brain stem. Brain herniation—no anticoagulants."

(b) (6)

49-Year-Old White Male, Meropenem VABP Arm

Cranial injury and ischemic stroke on admission. Acute thrombosis right humeral and ulnar vein Day 3, treatment with 7 days of heparin. Completed 9 days of treatment. Hemorrhagic transformation of ischemic stroke, extensive right hemisphere of the brain on Day 11. Hemorrhagic transformation stroke—heparin (BEMIPARIN). NO NARRATIVE, NO CRF submitted.

(b) (6)

42-Year-Old White Male, Meropenem VABP Arm

Admitted with hemorrhagic stroke on Day (b) (6) Completed 5 days of treatment. Progression of hemorrhage stroke on Day 5. Hemorrhagic stroke - No anticoagulants.

(b) (6)

45-Year-Old White Male, Ceftolozane/Tazobactam Ventilated HABP Arm

"Admission diagnosis not recorded. Admitted Day (b) (6), on Day -1 intubated due to pneumonia and breathing difficulty due to cerebral injury. On Day 4 of treatment acute renal failure, dose reduced. Treatment Day 1 through 5. On Day (b) (6) hemorrhagic stroke. Death on Day (b) (6). Outcome of index disease - hemorrhagic stroke. No anticoagulants. On tranexamic acid (to prevent excessive blood loss). *Dose decreased*"

(b) (6)

64-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

"Cerebral hemorrhage on admission, Day -9. Last dose of Ceftolozane on Day 9. Test of cure 'cure.' On Day 20 worsening of intracranial hemorrhage, severe, died on Day (b) (6) Hemorrhage intracranial—no anticoagulants."

(b) (6)

72-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

"Ischemic stroke on admission. Pulmonary embolism on Day 5. Intracerebral bleeding on Day 6, Renal failure on Day 6, drug discontinued on Day 7 (7 days of treatment).
PT: Cerebral hemorrhage. Renal failure NADROXAPARIN ALTEPLASE HEPARIN, full anticoagulation likely contributing to worsening bleeding. *Dose decreased to 1500*"

(b) (6)

69-Year-Old White Female, Ceftolozane/Tazobactam VABP Arm

Cerebral hemorrhage on admission on Day -7. Reported: Intracerebral bleeding severe on Day 10. Received 9 days of treatment. Test of cure, "cure." Dictionary derived: Cerebral hemorrhage. Nadroparin for prophylaxis of deep venous thrombosis Day 1 to 9.

(b) (6)

54-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

"Cerebral hemorrhage on admission Day -4. Tx: Completed 9 days of treatment. Clinical 'cure' at test of cure visit. Reported: New episode of intracerebral hemorrhage Day 30.

Dictionary derived: Cerebral hemorrhage. ENOXAPARIN prophylaxis."

(b) (6)

67-Year-Old Race Not Reported Male, Ceftolozane/Tazobactam VABP Arm

Ischemic stroke on admission on Day-4, thrombectomy performed. Reported and dictionary derived: hemorrhagic stroke on Day (b) (6) died on that day. Last dose of Ceftolozane on Day 9. Test of cure, 'cure.' ENOXAPARIN HEPARIN prophylaxis doses.

(b) (6)

24-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

Craniocerebral traumatic injury on Day -3. Subarachnoid hemorrhage, subarachnoid hemorrhage Day 4. Last day of medication on Day (b) (6), died on same day cardiorespiratory arrest, no autopsy. No anticoagulants.

(b) (6)

38-Year-Old Asian Male, Ceftolozane/Tazobactam VABP Arm

Day -15 cerebral hemorrhage on admission. On Day 15 last dose of Ceftolozane. Severe uncal herniation secondary to *cerebrovascular bleed left basal ganglia* and Temporoparietal Area on Day 22.

(b) (6)

67-Year-Old Asian Male, Ceftolozane/Tazobactam VABP Arm

Brain stem hemorrhage on admission. Uncal herniation. Last dose on Day 3. Brain herniation on Day 3.

(b) (6)

56-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

Cerebral hematoma on admission. Craniotomy Day -8. Gemotamponada ventricles of the brain, last dose on Day 3. Intraventricular hemorrhage on Day 5. Cure "indeterminate" at test of cure. No anticoagulants.

(b) (6)

25-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

"Completed 12 days of treatment. Hematoma to the right frontal lobe on Day 18. Cerebral hematoma.

Platelet count increased—no anticoagulants. Lost to follow-up, NO NARRATIVE, NO CRF submitted."

(b) (6)

30-Year-Old Black/African American Male, Ceftolozane/Tazobactam VABP Arm

Day -5 parietal skull fracture on admission due to traffic accident trauma. Cerebral herniation - brain herniation Day (b) (6) due to preexisting injuries, death on Day (b) (6) No specific mention of hemorrhage as cause of brain herniation, although possible due to parietal fracture.

(b) (6)

75-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

"Exacerbation of the closed craniotomy." Admitted Day (b) (6) intubated on Day -3 for craniotomy. Reported term: Progression of subdural hematoma of the left hemisphere on Day 4, drug stopped on Day 4. Subdural hematoma. No anticoagulants. Severe brain oedema SAE."

(b) (6)

68-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

Hemorrhagic stroke left thalamic region on admission, on Day -8, drained. Progression of hemorrhage stroke, Day 4 severe brain oedema and coma. Received 15 days of treatment and died on Day (b) (6) Clinical "cure" at test of cure. ENOXAPARIN prophylaxis without dates of administration.

(b) (6)

54-Year-Old White Female, Ceftolozane/Tazobactam VABP Arm

Cerebral hemorrhage (extradural hematoma) and craniotomy on admission at Day -6. Completed 9 days of treatment on Day 9. Severe intra-cerebral hemorrhage on Day 35. Clinical cure at test of cure at Day 16. Cerebral hemorrhage 26 days after last dose of Ceftolozane. On heparin deep vein thrombosis prophylaxis Day -3 to Day 18.

(b) (6)

75-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

Fall and cerebral hemorrhage on admission at Day -4. Transaminases X3 on Day 3. Infarction in posterior circulation distribution. Ischemic cerebral infarction. Worsening subarachnoid, subdural, and intraventricular hemorrhage on Day 4, last dose on Day 4. LRT no growth, end of treatment on Day 4 clinical outcome "undetermined." Died on Day (b) (6) Heparin prophylaxis.

(b) (6)

59-Year-Old White Male, Ceftolozane/Tazobactam VABP Arm

Cerebral ischemia on Day (b) (6). No death flag, no narrative, no CRF. Hemorrhage not confirmed.

(b) (6)

50-Year-Old White Female, Ceftolozane/Tazobactam VABP Arm

Subdural hematoma Day -3. anemia, liver failure, CV failure. On Day 6 of treatment hemorrhagic stroke diagnosis: cerebral hematoma evacuated on Day 6, bleeding tracheostomy, worsening liver failure. Last dose on Day 7, died on Day (b) (6) Cerebral hematoma and brain oedema reported SAEs—no anticoagulants.

15.6. Clinical Microbiology Review

Activity in vitro

Antibacterial activity

The tables below summarize the in vitro activity for the organisms associated with the HABP/VABP indication. Information presented was pooled from surveillance (2015-2017) and the Phase 3 study. The number of organisms, and the in vitro activity of ceftolozane/tazobactam against isolates from the United States were also taken into consideration when determining whether ceftolozane/tazobactam had activity against particular pathogens.

The in vitro activity of ceftolozane/tazobactam against indicated pathogens in the Applicant's proposed first list are in the table below. The majority of *H. influenzae* isolates fell within the MIC range of ≤0.064-8 mcg/mL; the MIC 90 for surveillance and clinical isolates was 0.125 mcg/mL. The MIC frequency distributions were similar between the 2015-2017 surveillance isolates and clinical trial isolates. Higher MICs among *P. aeruginosa* and Enterobacteriaceae were noted among European isolates compared to US isolates.

Table 72. In Vitro Activity of ceftolozane/tazobactam Against Indicated Pathogens Listed in the Applicant's Proposed First List

Pathogen	N (Surveillance/ Clinical)	MIC90 (mcg/mL)	MIC Range (mcg/mL)
P. aeruginosa	2657/ 155	0.25	0.125-≥32
Enterobacteriaceae	11579/ 430	0.06	0.06-≥ 32
H. influenzae	162/ 42	0.125	≤0.064-8

Source: Reviewer's table adapted from sources.
Taken from MIC distributions for ceftolozane/tazobactam from PN008 and 2015-2017 US Surveillance.

Clinical Microbiology Reviewer's Comment:
It is noted that *K. aerogenes* and *K. pneumoniae* are organisms that the Applicant proposed to add to the first list for this efficacy supplement relative to the currently approved labeling for ceftolozane/tazobactam. The information submitted was generally acceptable; however, please note the additional discussion related to *Klebsiella aerogenes* below. Three organisms (*Enterobacter cloacae*, *K. pneumoniae* and *Serratia marcescens*) proposed by the Applicant for the first list were noted to have MIC90 values that were above the proposed breakpoint for Enterobacteriaceae by surveillance and/or among baseline clinical trial isolates. Inclusion of these organisms in the lists was based on clinical trial data from the HABP/VABP trial and in other indications. One organism, *Klebsiella aerogenes* (formerly, *Enterobacter aerogenes*) did not have an adequate number of organisms for the first list (8), but had an MIC90 below the

proposed breakpoint for Enterobacteriaceae. This organism was found to be adequate for the second list based on in vitro data.

The Applicant also provided in vitro activity on 166 isolates of *Acinetobacter* spp. The overall MICs for the clinical trial isolates were higher compared to that of US surveillance studies, and higher than what is required for inclusion in the second list. Therefore, based on the information reviewed, these organisms do not qualify for being included in the first or second list. Baseline MIC90 for lower respiratory tract infection isolates of *K. pneumoniae* were also higher at 128 mcg/mL (N=175) compared to 2 mcg/mL (N=2979) for surveillance isolates.

15.6.1. Mechanism of Action and Mechanisms of Resistance

No new studies on mechanism of action or mechanisms of resistance were submitted in this NDA.

Susceptibility Testing Methods

Susceptibility testing was performed by Kirby-Bauer disk diffusion and broth microdilution methods on study isolates using fixed 4 mcg/mL tazobactam. To support the microbiology objectives in study CXA-NP-11-04, (b) (4) were responsible for the identification and antimicrobial susceptibility testing of clinical study isolates and quality control. Antimicrobial susceptibility testing was performed by two methods broth microdilution and disk diffusion. Validated American Type Culture Collection (ATCC) strains were tested concurrently with study isolates. Broth microdilution and disk diffusion methods were tested in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines for ceftolozane/tazobactam and meropenem.

Disk Manufacturers

Ceftolozane/tazobactam (30mcg/10mcg) combination disks were manufactured by (b) (4). AST disk diffusion and QC testing were performed according to CLSI guidelines and ACM US standard operating procedures.

Quality Control for Susceptibility Testing

Studies conducted to establish QC ranges for the *in vitro* susceptibility testing of ceftolozane/tazobactam were performed by the Applicant in accordance with guidelines established by CLSI (CLSI M23).

15.6.2. Activity in Vivo (Animal Studies)

The Applicant evaluated the activity of ceftolozane/tazobactam against. *K. pneumoniae* in a delayed treatment neutropenic mouse lung infection model using clinically relevant exposures of ceftolozane/tazobactam (Study PD0MM KW-0081). The animal models are described below.

Neutropenic Mouse Lung Infection Model

Ceftolozane/tazobactam was administered subcutaneously 2 hours after infectious challenge to approximate concentrations of ceftolozane and tazobactam in epithelial lining fluid (ELF) of patients, and every 2 hours thereafter. Efficacy was defined by ≥1 log10 colony-forming units per gram decrease in lung bacterial burden 26 hours post infection relative to pretreatment. It was determined that a humanized ceftolozane/tazobactam dose of 125/62.5 mg/kg was required to provide significant efficacy in this model. The bacterial strain information is shown in the table below:

Table 73. Bacterial Strain Information of Clinical Isolates Used in the Mouse Models of Pneumonia

Organism	Species	TOL/TAZ MIC (µg/mL)	β-lactamase and porin status
733390	*K. pneumoniae*	256	SHV-OSBL; TEM-OSBL; CTX-M-14; OmpK35 mutation; OmpK36 mutation
ATCC700603	*K. pneumoniae*	1	Not available
636298	*K. pneumoniae*	2	SHV-OSBL; TEM-OSBL; CTX-M-14; DHA-TYPE; OmpK35 mutation
938449	*K. pneumoniae*	4 [1]	SHV-OSBL; CTX-M-14
812581	*K. pneumoniae*	1	SHV-OSBL; CTX-M-15; OmpK35 deletion, OmpK36 mutation

MIC = minimum inhibitory concentration; MIC_{80} = concentration of drug at which 80% inhibition of bacterial growth is observed; µg/mL = microgram per milliliter

[1] There was no clear endpoint to 256 µg/mL, therefore the MIC_{80} of 4 µg/mL was used to evaluate bactericidal efficacy.

Source: [Ref. 5.3.5.4: 052T99]

Clinical Microbiology Reviewer's Comment:
Efficacy was demonstrated against 3 *K. pneumoniae* strains with ceftolozane/tazobactam MICs at or near the current breakpoint for Enterobacteriaceae. The isolates used in the animal models above had one or more beta-lactamase and some had porin mutations. One strain had a large difference in susceptibility to ceftolozane/tazobactam (1 versus 256 mcg/mL).

The Applicant reported that the combination of ceftolozane-tazobactam was active against all *K. pneumoniae* strains. However, only against the *K. pneumonia* 733390, 636298, 938449 and 812581 did the addition of tazobactam to ceftolozane increase bacterial burden reduction at the higher dose (125/62.5). *K. pneumoniae* isolate 733390 had a high MIC to ceftolozane/tazobactam (256 mcg/mL) but showed a 1.6-2 log CFU/g reduction in lung bacterial burden with ceftolozane/tazobactam treatment relative to pretreatment controls. The reason for efficacy was not further explained by the Applicant. Strains ATCC 700603 and 853258 did not have any further efficacy with addition of tazobactam. Additional reduction at lower dose

was observed against *K. pneumonia* 733390 and 812581 as well. Comparators of polymyxin B and tigecycline were used in the studies. At 26 h post-infection, 2h after the last treatment, or when animals reached the ethical severity endpoint (whichever came first), the clinical condition of all remaining animals was assessed. Immediately following confirmation of death, lungs were removed and weighed.

Clinical Microbiology Reviewer's Comment:
It is unknown why efficacy was not demonstrated with *K. pneumoniae* strains ATCC 700603 and 853258. It is possible that the strains contained beta lactamases that were not of the type inhibited by tazobactam. Information on the beta-lactamase and porin status of strain ATCC 700603 was not provided by the Applicant, however, the American Type Culture Collection describes is as a urine isolate that has SHV-18, an extended-spectrum beta-lactamase. For ATCC 812581 the Applicant described the following beta-lactamases and porin mutations: SHV-OSBL, CTX-M-15, Ompk35 deletion, Ompk36 mutation. The term OSBL is likely used by the Applicant to describe "older spectrum" (Sanders et al.; 2002) as opposed to extended-spectrum beta-lactamase activity (e.g. SHV-1).

The following tables summarized the pulmonary infection model experiments done by the Applicant:

Table 74. Outcome of Delayed Treatment Pulmonary Infection Model Experiments

Study ID	Org.	[1]TOL/TAZ MIC (µg/mL)	Infectious challenge (CFU/mouse)	Treatment			[2]Lung bacterial burden (Log_{10} CFU/g)			[3]*P*-value	
				Test article	Dose (mg/kg)	Freq.	Mean ± SD	Change from vehicle	Change from pretreatment	vs. vehicle	vs. pretreatment
EVT06988_ENTTB002	*K. pneumoniae* 733390	256	6.93×10^5	Pretreatment	NA	NA	6.85 ± 0.23	-2.11	NA	ND	NA
				Vehicle	NA	q2h	8.95 ± 1.48	NA	+2.11	NA	*p*=0.0152
				TOL/TAZ	125/62.5	q2h	4.36 ± 1.07	-4.60	-2.49	*p*=0.0001	*p*=0.0042
				TOL/TAZ	62.5/31.25	q2h	5.91 ± 0.28	-3.04	-0.94	*p*=0.0001	*p*=0.4055
EVT06988_ENTTB004			7.07×10^5	Pretreatment	NA	NA	6.77 ± 0.76	-2.61	NA	ND	NA
				Vehicle	NA	q2h	9.38 ± 0.19	NA	+2.61	NA	*p*=0.0001
				TOL	125	q2h	7.86 ± 0.79	-1.52	+1.08	*p*=0.0044	*p*=0.0738
				TOL/TAZ	125/31.25	q2h	5.17 ± 0.50	-4.21	-1.61	*p*=0.0001	*p*=0.0037
				TOL/TAZ	125/15.6	q2h	5.01 ± 0.69	-4.37	-1.76	*p*=0.0001	*p*=0.0014
				TOL	62.5	q2h	7.67 ± 0.62	-1.71	+0.89	*p*=0.0013	*p*=0.1859
				TOL/TAZ	62.5/15.6	q2h	5.91 ± 0.27	-3.47	-0.86	*p*=0.0001	*p*=0.2101
				TOL/TAZ	62.5/7.8	q2h	6.39 ± 0.41	-2.99	-0.39	*p*=0.0001	*p*=0.8888
EVT06988_ENTTB005	*K. pneumoniae* ATCC700603	1	9.07×10^4	Pretreatment	NA	NA	6.18 ± 0.18	-3.04	NA	ND	NA
				Vehicle	NA	q2h	9.22 ± 0.12	NA	+3.04	NA	*p*=0.0001
				TOL/TAZ	125/62.5	q2h	4.34 ± 0.51	-4.88	-1.84	*p*=0.0001	*p*=0.0001
				TOL/TAZ	62.5/31.25	q2h	4.37 ± 0.34	-4.85	-1.81	*p*=0.0001	*p*=0.0001
				TOL	125	q2h	4.22 ± 0.19	-4.99	-1.96	*p*=0.0001	*p*=0.0001
				TOL	62.5	q2h	3.35 ± 0.66	-5.87	-2.83	*p*=0.0001	*p*=0.0001

Table 10 Outcome of Delayed Treatment Pulmonary Infection Model Experiments

Study ID	Org.	[1]TOL/TAZ MIC (µg/mL)	Infectious challenge (CFU/mouse)	Treatment			[2]Lung bacterial burden (Log_{10} CFU/g)			[3]*P*-value	
				Test article	Dose (mg/kg)	Freq.	Mean ± SD	Change from vehicle	Change from pretreatment	vs. vehicle	vs. pretreatment
EVT06988_ENTTB006	*K. pneumoniae* 636298	2	3.47×10^5	Pretreatment	NA	NA	5.55 ± 0.94	-4.03	NA	ND	NA
				Vehicle	NA	q2h	9.58 ± 0.57	NA	+4.03	NA	*p*=0.0001
				TOL/TAZ	125/62.5	q2h	4.87 ± 0.99	-4.71	-0.68	*p*=0.0001	*p*=0.7662
				TOL/TAZ	62.5/31.25	q2h	5.71 ± 0.14	-3.87	+0.16	*p*=0.0001	*p*=0.9996
				Tigecycline	45	q8h	5.35 ± 1.19	-4.23	-0.20	*p*=0.0001	*p*=0.9996
				TOL	125	q2h	5.73 ± 1.22	-3.85	+0.18	*p*=0.0001	*p*=0.9996
				TOL	62.5	q2h	6.38 ± 1.26	-3.20	+0.83	*p*=0.0001	*p*=0.6050
EVT06988_ENTTB007	*K. pneumoniae* 938449	[4]4	6.8×10^5	Pretreatment	NA	NA	7.07 ± 0.13	-2.65	NA	ND	NA
				Vehicle	NA	q2h	9.72 ± 0.34	NA	+2.65	NA	*p*=0.0001
				TOL/TAZ	125/62.5	q2h	4.92 ± 0.57	-4.80	-2.15	*p*=0.0001	*p*=0.0001
				TOL/TAZ	62.5/31.25	q2h	5.80 ± 0.65	-3.92	-1.27	*p*=0.0001	*p*=0.0010
				Tigecycline	45	q8h	7.96 ± 0.37	-1.76	+0.89	*p*=0.0001	*p*=0.0498
				TOL	62.5	q2h	6.05 ± 0.44	-3.67	-1.02	*p*=0.0001	*p*=0.0087
				TOL	125	q2h	5.84 ± 0.41	-3.88	-1.23	*p*=0.0001	*p*=0.0021

Table 10 Outcome of Delayed Treatment Pulmonary Infection Model Experiments

Study ID	Org.	[1]TOL/TAZ MIC (µg/mL)	Infectious challenge (CFU/mouse)	Treatment			[2]Lung bacterial burden (Log_{10} CFU/g)			[3]*P*-value	
				Test article	Dose (mg/kg)	Freq.	Mean ± SD	Change from vehicle	Change from pretreatment	vs. vehicle	vs. pretreatment
EVT06988_ENTTB009	*K. pneumoniae* 812581	1	7.87×10^5	Pretreatment	NA	NA	6.57 ± 0.10	-3.80	NA	ND	NA
				Vehicle	NA	q2h	10.37 ± 0.51	NA	+3.80	NA	*p*=0.0001
				TOL/TAZ	125/62.5	q2h	4.23 ± 0.22	-6.14	-2.34	*p*=0.0001	*p*=0.0023
				TOL/TAZ	62.5/31.25	q2h	4.27 ± 0.72	-6.10	-2.31	*p*=0.0001	*p*=0.0027
				Tigecycline	45	q8h	5.76 ± 0.43	-4.61	-0.81	*p*=0.0001	*p*=0.6487
				TOL	125	q2h	5.79 ± 1.00	-4.58	-0.79	*p*=0.0001	*p*=0.6313
				TOL	62.5	q2h	6.84 ± 1.97	-3.53	+0.27	*p*=0.0001	*p*=0.9949

[1] The listed TOL/TAZ MIC corresponds to the one determined experimentally at Merck Research Laboratories ([Table 4]).

[2] Lung bacterial burden was assessed prior to treatment start, 2 hours after infectious challenge. All other lung bacterial burden measurements were taken 26 hours after infectious challenge.

[3] Significance was determined by one-way analysis of variance with Dunnett's post-hoc test for multiple comparisons. Bolded *p*-values indicate significance ($p < 0.05$).

[4] There was no clear endpoint to 256 µg/mL, therefore the MIC_{80} of 4 µg/mL was used to evaluate bactericidal efficacy.

CFU = colony-forming units; Freq. = frequency; ID = identification; µg/mL = microgram per milliliter; MIC = minimum inhibitory concentration; MIC_{80} = concentration of drug at which 80% inhibition of bacterial growth is observed; mg/kg = milligram per kilogram; NA = not applicable; ND = not determined; Org. = organism; SD = standard deviation; TOL = ceftolozane; TAZ = tazobactam

The relationship of susceptibility to efficacy is shown in the table below.

Table 75. Relationship of In Vitro Susceptibility to Efficacy in Lung Infection Studies

Organism	TOL/TAZ MIC (µg/mL)	[1]No. of isolates that demonstrated efficacy at indicated TOL/TAZ doses	
		125/62.5 mg/kg	62.5/31.25 mg/kg
K. pneumoniae	1	2 of 2	2 of 2
	2	0 of 1	0 of 1
	4	1 of 1	1 of 1
	256	1 of 1	0 of 1

[1] Efficacy was defined by a significant ≥ 1 log CFU/g decrease in lung bacterial burden 26 hours post treatment relative to pretreatment in experiments shown in [Table 10].

CFU/g = colony-forming units per gram; MIC = minimum inhibitory concentration; no. = number; TOL = ceftolozane; TAZ = tazobactam

Clinical Microbiology Reviewer's Comment:

Ceftolozane/tazobactam showed efficacy in the murine models described above at levels comparable or greater than ceftolozane alone depending on the isolate tested.

Pharmacokinetics/Pharmacodynamics

In vitro models

Twice the currently approved dose for the treatment of cIAI and cUTI was proposed by the Applicant for the new indication for the treatment of HABP/VABP. This was to provide sufficient exposure in the lung. Two additional studies were completed since the original application PN018 and PN007 to provide further justification for the dose regimen in addition to what was submitted in the original application for cUTI/cIAI.

An in vitro hollow fiber culture cell system ((b) (4)) was used to describe time-kill for ceftolozane/tazobactam against 21 *P. aeruginosa* and Enterobacteriaceae strains. Ceftolozane/tazobactam MIC was determined by checkerboard assay; and bacterial isolates producing one or more beta-lactamases were used in this study. For *P. aeruginosa* the predominant isolates were characterized for PDC beta lactamase. An objective of the Applicant was to demonstrate the projected efficacy of the 3 g ceftolozane/tazobactam dose against clinical isolates at or near the current minimum inhibitory concentration (MIC) susceptible breakpoints of 4/4 mcg/mL for *P. aeruginosa* and 2/4 mcg/mL for Enterobacteriaceae. Bacteria were exposed to ceftolozane/tazobactam at concentrations the Applicant reported to simulate exposures in the Epithelial Lining Fluid (ELF). Efficacy was defined as a 3-log decrease in colony forming units per milliliter (CFU/mL) from starting inoculum with no growth after 69 hours. The results are summarized in the table below. Based on these results, the Applicant is proposing that CLSI breakpoints for Enterobacteriaceae remain the same at 2/4 mcg/mL for Enterobacteriaceae.

Table 76: Number of Strains in Which TOL/TAZ Demonstrated Efficacy in Hollow Fiber Studies at Steady-state Lung Epithelial Lining Fluid Pharmacokinetic Profiles for TOL TAZ

Organism	TOL/TAZ MIC (µg/mL)			
	2	4	8	>8 [1]
P. aeruginosa	NA	4 of 4	3 of 4	NA
K. pneumoniae	0 of 1	3 of 4	0 of 1	0 of 3
E. coli	0 of 1	NA	0 of 2	1 of 1

MIC = minimum inhibitory concentration; NA = not applicable; TOL = ceftolozane; TAZ = tazobactam
[1] Strains included in the >8 µg/mL MIC included strains with an MIC of 8 to 16 µg/mL.

Source: [Ref. 5.3.5.4: 052NL5]

In separate experiments, the hollow fiber system was used to evaluate the activity of PK exposures corresponding to levels in ELF estimated through observed plasma drug concentrations in critically ill pneumonia patients that received clinical doses of ceftolozane and tazobactam, corrected for lung penetration issues. Efficacy was evaluated against 13 strains of *K. pneumoniae* and 2 strains of *E. coli*. Efficacy was seen at higher MICs than the hollow fiber experiments that simulated steady state (SS)-ELF drug concentrations. The Applicant considers

the studies from the hollow fiber experiments simulating the SS-ELF drug concentrations to better mimic the scenario in the lung.

Clinical Microbiology Reviewer's Comment:
The Applicant stated that efficacy was observed in the in vitro hollow fiber model against *P. aeruginosa* up to the ceftolozane/tazobactam breakpoint of 4/4mcg/mL and 2/4 mcg/mL for Enterobacteriaceae. In the neutropenic mouse lung infection model, the efficacy was observed in *K. pneumoniae* isolates with ceftolozane/tazobactam MIC of 4mcg/mL and for Enterobacteriaceae 2/4 mcg/mL. These studies appear to be supportive of the Applicant's proposed MIC breakpoints for *P. aeruginosa* and Enterobacteriaceae. The Agency's Clinical Pharmacology review team also determined through analysis of the probability of target attainment, that the proposed MIC breakpoints can be supported. See the Clinical Pharmacology section for additional information.

15.6.3. Clinical Microbiology Analyses of Efficacy

The Phase 3 study was titled, "A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Pneumonia".
The primary and secondary efficacy outcomes for the study were clinical in nature (all-cause mortality and clinical response at TOC). The primary efficacy analysis population was the ITT population and the secondary microbiological endpoints were assessed in the mITT or ME populations. The mITT population comprised of 511 subjects and was a subset of the ITT defined by the Applicant as follows: population that received any amount of study drug and had at least one bacterial respiratory pathogen isolate from the baseline lower respiratory culture that is susceptible to at least one study drug. See the Agency's Clinical and Statistical review for additional information on these populations as the mITT population was subsequently defined as the population that received any amount of study drug and had at least one bacterial respiratory pathogen isolated from the baseline lower respiratory culture that was susceptible to the comparator, meropenem. Subjects with a non-streptococcal Gram-positive pathogen as their only baseline pathogen were excluded from the mITT population.

The ME population was 233 subjects and is a subset of the mITT population that included patients who had an evaluable clinical outcome and one baseline respiratory pathogen isolated from baseline LRT culture that was susceptible to at least one study drug. To be eligible for the ME population the bacterial count had to be quantitative at levels of $\geq 10^5$ CFU/mL for endotracheal aspirates (ETA), $\geq 10^4$ CFU/mL for bronchoalveolar lavage (BAL)/mini-BAL, and $\geq 10^3$ CFU/mL for phosphate buffered saline (PBS). Both treatment groups demonstrated per-pathogen microbiological eradication rates at the TOC visit against commonly isolated pathogens including *P. aeruginosa* (74.6% versus 63.1%), Enterobacteriaceae (74.4% versus 69.7%) and *H. influenzae* (90.9% versus 68.8%) for ceftolozane/tazobactam and meropenem arms, respectively.

Baseline infecting pathogens were isolated from a quantitative LRT culture and were tested for susceptibility to ceftolozane/tazobactam and meropenem using provisional breakpoints. Baseline pathogens were considered susceptible to ceftolozane/tazobactam if the MIC value was ≤4 mcg/mL for Enterobacteriaceae, or ≤8 mcg/mL for *P. aeruginosa* and other bacteria such as *H. influenzae*. The MIC cut-off values for susceptibility to meropenem were based on CLSI definitions and were ≤1 mcg/mL for Enterobacteriaceae, ≤2 mcg/mL for *P. aeruginosa,* and ≤0.5 mcg/mL for *H. influenzae*.

Clinical Microbiology Reviewer's Comment:
The criteria above have been reevaluated by the Agency. This included whether susceptibility to ceftolozane/tazobactam and/or meropenem should be used for inclusion in the mITT population, what organisms should be excluded and the breakpoints for the organisms. It was decided along with the clinical team that although *S. aureus* is not listed in the labeling, it should be included in the analysis of polymicrobial infection since it is a significant pathogen for the indication. The definition of susceptibility for ceftolozane/tazobactam included organisms in the intermediate range by FDA breakpoints; therefore, the outcome by MIC per pathogen was considered when analyzing the data. It was also noted that some gram-negative pathogens were excluded from analysis and when questioned, the Applicant clarified that pathogens from 10 subjects were excluded from the mITT population since the samples were collected outside of the protocol-allowed-window of 36 hours.

Specimens for Culture

Local or regional laboratories from clinical study sites were responsible for primary identification of pathogens isolated from lower respiratory tract specimens in study CXA-NP-11-04. All pathogens were shipped to ACM regional Laboratories (Singapore or York, United Kingdom) or directly to ACM US using approved carriers. Clinical study isolates were sent from ACM Regional Laboratories to ACM US where they underwent re-identification, antimicrobial susceptibility testing for selected antimicrobials and archival storage. QC testing was performed each day subject isolates were tested.

If a discrepancy existed regarding organism identification at the species level between the site and the central microbiology laboratory, the central microbiology laboratory data were used. If the discrepancy was at the genus level, both organisms were included. If no central laboratory data existed, local data were used. For each distinct pathogen identified for a subject, if the organism was cultured on more than one occasion per visit or 2 strains of the same species were isolated, a representative isolate was selected for use in all microbiological analyses requiring isolate-specific information. This isolate was selected using a hierarchical algorithm until a single isolate remained. As some of the criteria included the selection of the organism with the higher MIC for ceftolozane/tazobactam or meropenem and was therefore more conservative, this reviewer found the criteria to be acceptable.

Microbiological Efficacy: Per-pathogen microbiological response categories were

defined in the study protocols as per-pathogen microbiological response, per-subject microbiological response and emergent infections.

The Applicant reported that baseline respiratory Gram-negative aerobic bacilli were isolated in (97.7%) of subjects in the mITT population. Endotracheal Aspirate (ETA) were the most common form of baseline lower respiratory tract collection methods. Monomicrobial respiratory tract infections were more common than polymicrobial infections and had to be redefined to include *S. aureus* as previously discussed. Following an information request to the company a new data set was provided for baseline lower respiratory tract pathogens including *S. aureus*. In the ceftolozane/tazobactam arm mortality rates by baseline LRT pathogens including *S. aureus* were 30/146 for monomicrobial, and 27/132 for polymicrobial; similar rates were observed in the meropenem arm (36/145 for monomicrobial and 30/125 for polymicrobial). The percentage mortality rate for Gram-negative pathogens only, Gram-negative and Gram-positive pathogens and Gram-positive pathogens only were also similar between treatment arms.

The Applicant reported that Enterobacteriaceae were isolated from 380 (74.2%) subjects. *K. pneumoniae* and *E. coli* were the most prevalent species of Enterobacteriaceae, isolated from 177 (34.6%) and 93 (18.2%) subjects, respectively. Among all 380 Enterobacteriaceae, 157 (41.3%) were ESBL-positive; among all 177 *K. pneumoniae* isolates, 105 (59.3%) were ESBL-positive. *Pseudomonas aeruginosa* was isolated from 128 (25%) subjects and was the second most prevalent pathogen. AmpC-overexpression among *P. aeruginosa* was detected in 15 (11.7%) of the subjects with *P. aeruginosa*. Other prominent pathogens included 38 (7.4%) subjects with *Acinetobacter baumannii* and 38 (7.4%) subjects with *H. influenzae*. The distribution of baseline respiratory pathogens in the ME population was comparable to that in the mITT population.

Molecular characterization

In study report MK-7625A PN008, the Applicant provided information on the molecular characterization of isolates from the HABP/VABP clinical trial. Bacterial isolates were collected from lower respiratory tract samples at screening and were evaluated by the Applicant for resistance mechanism testing if the isolates met a set of pre-defined criteria.
Among the 262 Enterobacteriaceae isolates tested, 61 carried genes encoding carbapenemases and 168 carried ESBL genes; a majority of these carried *bla*CTX-M (165/168). The activity of ceftolozane/tazobactam was limited against isolates carrying carbapenemases and some *K. pneumoniae* harboring ESBL genes. OmpK35/36 gene mutations among resistant Enterobacteriaceae isolates were not assessed by the Applicant.

Among the 89 *P. aeruginosa* isolates, carbapenemases and ESBL-encoding genes were observed among 12 and 22 isolates, respectively. Ceftolozane/tazobactam showed in vitro activity against isolates carrying certain GES and PME genes, but not those carrying genes encoding VIM, VEB, PER, and some CTX-Ms. *P. aeruginosa* isolates displaying elevated

expression of AmpC (21 isolates, regardless of PDC allele), elevated expression of efflux pumps (9 isolates), and/or loss of OprD (47 isolates).

Clinical Microbiology Reviewer's Comment:
It is noted that ceftolozane/tazobactam does not have activity against all forms of GES. For example, GES-6 can lead to resistance to ceftolozane-tazobactam combination in *P. aeruginosa* (Poirel, et al. 2019) and that there are new resistance reports in the literature of cases of *P. aeruginosa* producing PDC beta lactamase variants that have increased resistance to ceftolozane/tazobactam (Barnes et al 2018, MacVane et al, 2017). The Applicant states that the *P. aeruginosa* isolates from HABP/VABP clinical trials that produced AmpC, elevated efflux pumps and loss of OprD were generally susceptible to ceftolozane/tazobactam, however, these virulence factors could be found among *P. aeruginosa* isolates with high and low MICs to ceftolozane/tazobactam. Following discussions with the Applicant, the statement was removed and a rationale was given, as stated in the Clinical Microbiology summary of this unireview above.

Clinical response evaluations were performed at the EOT visit, TOC visit (7 to 14 days after EOT), and the LFU visit (28 to 35 days after EOT). Microbiological assessments, based on collection of quantitative LRT cultures, occurred at the EOT and TOC visits.

Data from the ME population was presented by the Applicant in addition to the mITT population, as this population is the subset of the mITT population that adhered to the protocol through the TOC visit. Any differences in the two populations noted by the Applicant, were not found by the Applicant to be statistically significant.

The clinical cure rate by baseline pathogen as evaluated by the Applicant at the TOC visit for the most common pathogens in PN008 (mITT population) as shown in the table below. It was noted that there were 84 K*. pneumoniae* isolates in the ceftolozane/tazobactam arm with most MICs at 0.25 (N=18) and 0.5 mcg/mL (N=14). There were 91 in the meropenem arm with most isolates between MICs 0.25 and 2 mcg/mL. Twenty-eight-day all-cause mortality and clinical cure rates by baseline pathogen from the Phase 3 study (TOC) of HABP and VABP (mITT) were evaluated by the Agency's Clinical and Statistical teams. See the Clinical section of the review and Table 14 of the proposed labeling for additional information.

Table 77. Summary of Per Pathogen (≥10 Isolates at Baseline) Clinical Response at Test of Cure Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264) N1	Cure n (%)	Failure n (%)	Meropenem (N=247) N1	Cure n (%)	Failure n (%)
Gram-Negative	< 0.064 - >= 256	255	155 (60.8)	100 (39.2)	238	135 (56.7)	103 (43.3)
	< 0.064	7	4 (57.1)	3 (42.9)	10	4 (40.0)	6 (60.0)
	0.064	0	0	0	3	2 (66.7)	1 (33.3)
	0.125	29	20 (69.0)	9 (31.0)	22	10 (45.5)	12 (54.5)
	0.25	80	50 (62.5)	30 (37.5)	71	39 (54.9)	32 (45.1)
	0.5	74	47 (63.5)	27 (36.5)	76	43 (56.6)	33 (43.4)
	1	41	26 (63.4)	15 (36.6)	50	33 (66.0)	17 (34.0)
	2	30	17 (56.7)	13 (43.3)	23	12 (52.2)	11 (47.8)
	4	23	13 (56.5)	10 (43.5)	10	6 (60.0)	4 (40.0)
	8	17	5 (29.4)	12 (70.6)	17	8 (47.1)	9 (52.9)
	16	8	3 (37.5)	5 (62.5)	8	4 (50.0)	4 (50.0)
	32	8	6 (75.0)	2 (25.0)	6	3 (50.0)	3 (50.0)
	64	10	7 (70.0)	3 (30.0)	7	5 (71.4)	2 (28.6)
	128	10	3 (30.0)	7 (70.0)	4	3 (75.0)	1 (25.0)
	>= 256	8	2 (25.0)	6 (75.0)	6	4 (66.7)	2 (33.3)
Pseudomonas aeruginosa	0.125 - >= 256	62	36 (58.1)	26 (41.9)	65	39 (60.0)	26 (40.0)
	0.125	0	0	0	1	1 (100.0)	0
	0.25	2	1 (50.0)	1 (50.0)	0	0	0
	0.5	24	15 (62.5)	9 (37.5)	26	15 (57.7)	11 (42.3)
	1	12	7 (58.3)	5 (41.7)	25	17 (68.0)	8 (32.0)
	2	18	11 (61.1)	7 (38.9)	10	4 (40.0)	6 (60.0)
	4	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)
	8	2	0	2 (100.0)	0	0	0
	32	2	1 (50.0)	1 (50.0)	0	0	0
	>= 256	1	0	1 (100.0)	1	1 (100.0)	0
AmpC Overexpressing Pseudomonas aeruginosa	1 - 8	9	4 (44.4)	5 (55.6)	6	3 (50.0)	3 (50.0)
	1	1	1 (100.0)	0	1	1 (100.0)	0
	2	7	3 (42.9)	4 (57.1)	2	0	2 (100.0)
	4	0	0	0	3	2 (66.7)	1 (33.3)
	8	1	0	1 (100.0)	0	0	0

Summary of Per-Pathogen (>= 10 Isolates at Baseline) Clinical Response at Test of Cure (TOC) Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264) N1	Cure n (%)	Failure n (%)	Meropenem (N=247) N1	Cure n (%)	Failure n (%)
Enterobacteriaceae	< 0.064 - >= 256	191	118 (61.8)	73 (38.2)	183	103 (56.3)	80 (43.7)
	< 0.064	0	0	0	1	1 (100.0)	0
	0.125	16	10 (62.5)	6 (37.5)	17	7 (41.2)	10 (58.8)
	0.25	74	45 (60.8)	29 (39.2)	66	35 (53.0)	31 (47.0)
	0.5	51	34 (66.7)	17 (33.3)	49	27 (55.1)	22 (44.9)
	1	23	14 (60.9)	9 (39.1)	21	14 (66.7)	7 (33.3)
	2	10	5 (50.0)	5 (50.0)	16	10 (62.5)	6 (37.5)
	4	15	8 (53.3)	7 (46.7)	7	4 (57.1)	3 (42.9)
	8	9	4 (44.4)	5 (55.6)	8	4 (50.0)	4 (50.0)
	16	8	3 (37.5)	5 (62.5)	8	4 (50.0)	4 (50.0)
	32	3	2 (66.7)	1 (33.3)	6	3 (50.0)	3 (50.0)
	64	9	7 (77.8)	2 (22.2)	6	4 (66.7)	2 (33.3)
	128	9	3 (33.3)	6 (66.7)	4	3 (75.0)	1 (25.0)
	>= 256	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)
ESBL+ Enterobacteriaceae	0.25 - >= 256	83	48 (57.8)	35 (42.2)	73	45 (61.6)	28 (38.4)
	0.25	6	3 (50.0)	3 (50.0)	6	4 (66.7)	2 (33.3)
	0.5	19	12 (63.2)	7 (36.8)	16	10 (62.5)	6 (37.5)
	1	11	8 (72.7)	3 (27.3)	14	9 (64.3)	5 (35.7)
	2	6	3 (50.0)	3 (50.0)	9	6 (66.7)	3 (33.3)
	4	12	7 (58.3)	5 (41.7)	7	4 (57.1)	3 (42.9)
	8	6	2 (33.3)	4 (66.7)	5	3 (60.0)	2 (40.0)
	16	8	3 (37.5)	5 (62.5)	7	4 (57.1)	3 (42.9)
	32	3	2 (66.7)	1 (33.3)	4	1 (25.0)	3 (75.0)
	64	8	6 (75.0)	2 (25.0)	6	4 (66.7)	2 (33.3)
	128	9	3 (33.3)	6 (66.7)	4	3 (75.0)	1 (25.0)
	>= 256	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)
Enterobacter cloacae	0.125 - 8	17	10 (58.8)	7 (41.2)	16	4 (25.0)	12 (75.0)
	0.125	2	1 (50.0)	1 (50.0)	1	0	1 (100.0)
	0.25	5	3 (60.0)	2 (40.0)	5	2 (40.0)	3 (60.0)
	0.5	6	3 (50.0)	3 (50.0)	7	2 (28.6)	5 (71.4)

Summary of Per-Pathogen (>= 10 Isolates at Baseline) Clinical Response at Test of Cure (TOC) Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category / Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264) N1	Cure n (%)	Failure n (%)	Meropenem (N=247) N1	Cure n (%)	Failure n (%)
	1	2	1 (50.0)	1 (50.0)	1	0	1 (100.0)
	2	0	0	0	1	0	1 (100.0)
	4	1	0	1 (100.0)	0	0	0
	8	2	2 (100.0)	0	2	0	2 (100.0)
ESBL+ Enterobacter cloacae	0.5 - 8	1	0	1 (100.0)	1	0	1 (100.0)
	0.5	1	0	1 (100.0)	0	0	0
	8	0	0	0	1	0	1 (100.0)
Escherichia coli	0.125 - 64	51	32 (62.7)	19 (37.3)	42	26 (61.9)	16 (38.1)
	0.125	7	4 (57.1)	3 (42.9)	8	4 (50.0)	4 (50.0)
	0.25	27	18 (66.7)	9 (33.3)	24	17 (70.8)	7 (29.2)
	0.5	8	5 (62.5)	3 (37.5)	6	2 (33.3)	4 (66.7)
	1	6	5 (83.3)	1 (16.7)	3	2 (66.7)	1 (33.3)
	2	0	0	0	1	1 (100.0)	0
	4	2	0	2 (100.0)	0	0	0
	64	1	0	1 (100.0)	0	0	0
ESBL+ Escherichia coli	0.25 - 64	20	11 (55.0)	9 (45.0)	10	5 (50.0)	5 (50.0)
	0.25	5	3 (60.0)	2 (40.0)	3	2 (66.7)	1 (33.3)
	0.5	7	4 (57.1)	3 (42.9)	5	2 (40.0)	3 (60.0)
	1	5	4 (80.0)	1 (20.0)	2	1 (50.0)	1 (50.0)
	4	2	0	2 (100.0)	0	0	0
	64	1	0	1 (100.0)	0	0	0
Klebsiella oxytoca	0.125 - 2	14	9 (64.3)	5 (35.7)	12	7 (58.3)	5 (41.7)
	0.125	3	2 (66.7)	1 (33.3)	1	0	1 (100.0)
	0.25	9	6 (66.7)	3 (33.3)	8	4 (50.0)	4 (50.0)
	0.5	1	1 (100.0)	0	2	2 (100.0)	0
	1	0	0	0	1	1 (100.0)	0
	2	1	0	1 (100.0)	0	0	0

Summary of Per-Pathogen (>= 10 Isolates at Baseline) Clinical Response at Test of Cure (TOC) Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category / Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264) N1	Cure n (%)	Failure n (%)	Meropenem (N=247) N1	Cure n (%)	Failure n (%)
ESBL+ Klebsiella oxytoca	0.25 - 1	0	0	0	3	2 (66.7)	1 (33.3)
	0.25	0	0	0	1	0	1 (100.0)
	0.5	0	0	0	1	1 (100.0)	0
	1	0	0	0	1	1 (100.0)	0
Klebsiella pneumoniae	0.125 - >= 256	84	51 (60.7)	33 (39.3)	91	58 (63.7)	33 (36.3)
	0.125	0	0	0	1	1 (100.0)	0
	0.25	18	8 (44.4)	10 (55.6)	23	12 (52.2)	11 (47.8)
	0.5	14	12 (85.7)	2 (14.3)	14	10 (71.4)	4 (28.6)
	1	8	6 (75.0)	2 (25.0)	11	8 (72.7)	3 (27.3)
	2	5	4 (80.0)	1 (20.0)	11	8 (72.7)	3 (27.3)
	4	7	5 (71.4)	2 (28.6)	5	3 (60.0)	2 (40.0)
	8	4	1 (25.0)	3 (75.0)	3	3 (100.0)	0
	16	7	3 (42.9)	4 (57.1)	7	4 (57.1)	3 (42.9)
	32	3	2 (66.7)	1 (33.3)	5	2 (40.0)	3 (60.0)
	64	8	7 (87.5)	1 (12.5)	6	4 (66.7)	2 (33.3)
	128	9	3 (33.3)	6 (66.7)	4	3 (75.0)	1 (25.0)
	>= 256	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)
ESBL+ Klebsiella pneumoniae	0.25 - >= 256	53	31 (58.5)	22 (41.5)	52	34 (65.4)	18 (34.6)
	0.25	1	0	1 (100.0)	2	2 (100.0)	0
	0.5	5	4 (80.0)	1 (20.0)	3	2 (66.7)	1 (33.3)
	1	6	5 (83.3)	1 (16.7)	8	5 (62.5)	3 (37.5)
	2	3	2 (66.7)	1 (33.3)	8	6 (75.0)	2 (25.0)
	4	6	4 (66.7)	2 (33.3)	5	3 (60.0)	2 (40.0)
	8	4	1 (25.0)	3 (75.0)	3	3 (100.0)	0
	16	7	3 (42.9)	4 (57.1)	7	4 (57.1)	3 (42.9)
	32	3	2 (66.7)	1 (33.3)	4	1 (25.0)	3 (75.0)
	64	7	6 (85.7)	1 (14.3)	6	4 (66.7)	2 (33.3)
	128	9	3 (33.3)	6 (66.7)	4	3 (75.0)	1 (25.0)
	>= 256	3	2 (66.7)	1 (33.3)	3	2 (66.7)	1 (33.3)

Summary of Per-Pathogen (>= 10 Isolates at Baseline) Clinical Response at Test of Cure (TOC) Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264)			Meropenem (N=247)		
		N1	Cure n (%)	Failure n (%)	N1	Cure n (%)	Failure n (%)
Proteus mirabilis	0.25 - 8	23	13 (56.5)	10 (43.5)	20	11 (55.0)	9 (45.0)
	0.25	4	3 (75.0)	1 (25.0)	2	0	2 (100.0)
	0.5	13	8 (61.5)	5 (38.5)	12	9 (75.0)	3 (25.0)
	1	2	0	2 (100.0)	3	2 (66.7)	1 (33.3)
	2	1	0	1 (100.0)	1	0	1 (100.0)
	4	2	2 (100.0)	0	0	0	0
	8	1	0	1 (100.0)	2	0	2 (100.0)
ESBL+ Proteus mirabilis	0.5 - 8	10	5 (50.0)	5 (50.0)	11	7 (63.6)	4 (36.4)
	0.5	5	3 (60.0)	2 (40.0)	6	5 (83.3)	1 (16.7)
	1	1	0	1 (100.0)	3	2 (66.7)	1 (33.3)
	2	1	0	1 (100.0)	1	0	1 (100.0)
	4	2	2 (100.0)	0	0	0	0
	8	1	0	1 (100.0)	1	0	1 (100.0)
Serratia marcescens	0.25 - 16	17	9 (52.9)	8 (47.1)	12	7 (58.3)	5 (41.7)
	0.25	1	1 (100.0)	0	1	1 (100.0)	0
	0.5	6	5 (83.3)	1 (16.7)	6	3 (50.0)	3 (50.0)
	1	3	1 (33.3)	2 (66.7)	2	1 (50.0)	1 (50.0)
	2	3	1 (33.3)	2 (66.7)	1	1 (100.0)	0
	4	1	0	1 (100.0)	2	1 (50.0)	1 (50.0)
	8	2	1 (50.0)	1 (50.0)	0	0	0
	16	1	0	1 (100.0)	0	0	0
ESBL+ Serratia marcescens	0.5 - 16	6	3 (50.0)	3 (50.0)	2	1 (50.0)	1 (50.0)
	0.5	1	1 (100.0)	0	0	0	0
	2	2	1 (50.0)	1 (50.0)	0	0	0
	4	1	0	1 (100.0)	2	1 (50.0)	1 (50.0)
	8	1	1 (100.0)	0	0	0	0
	16	1	0	1 (100.0)	0	0	0
Acinetobacter baumannii	< 0.064 - >= 256	24	7 (29.2)	17 (70.8)	14	6 (42.9)	8 (57.1)

Summary of Per-Pathogen (>= 10 Isolates at Baseline) Clinical Response at Test of Cure (TOC) Visit by Ceftolozane/Tazobactam Baseline MIC (mITT Population)

Baseline Pathogen Category Baseline Pathogen	Ceftolozane /Tazobactam Baseline MIC (µg/ml)	Ceftolozane/Tazobactam (N=264)			Meropenem (N=247)		
		N1	Cure n (%)	Failure n (%)	N1	Cure n (%)	Failure n (%)
	< 0.064	2	0	2 (100.0)	1	0	1 (100.0)
	0.25	0	0	0	3	1 (33.3)	2 (66.7)
	0.5	3	1 (33.3)	2 (66.7)	1	1 (100.0)	0
	1	2	2 (100.0)	0	2	2 (100.0)	0
	2	3	2 (66.7)	1 (33.3)	0	0	0
	4	3	1 (33.3)	2 (66.7)	0	0	0
	8	7	1 (14.3)	6 (85.7)	5	1 (20.0)	4 (80.0)
	>= 256	4	0	4 (100.0)	2	1 (50.0)	1 (50.0)
Haemophilus influenzae	< 0.064 - 8	22	19 (86.4)	3 (13.6)	15	8 (53.3)	7 (46.7)
	< 0.064	3	3 (100.0)	0	3	1 (33.3)	2 (66.7)
	0.064	0	0	0	1	0	1 (100.0)
	0.125	11	10 (90.9)	1 (9.1)	3	2 (66.7)	1 (33.3)
	0.25	6	5 (83.3)	1 (16.7)	5	3 (60.0)	2 (40.0)
	0.5	2	1 (50.0)	1 (50.0)	2	1 (50.0)	1 (50.0)
	8	0	0	0	1	1 (100.0)	0

Notes: n=Number of subjects within a specific response category. N=Number of subjects in specific population. N1= Number of subjects within a specific baseline MIC.
Percents are calculated as 100 x (n/N1). ESBL+ includes any ESBL enzyme. Treatment Failure Approach (TFA) is used for this analysis.
TFA: Subjects with missing clinical responses are considered failures. For subjects with clinical failure response at EOT, they are counted in failure category at TOC.

Source: [P008MK7625A: analysis-adsl; admb; adms]

Clinical Microbiology Reviewer's Comment:
This information was reviewed for whether the pathogens should be included in first list in microbiology section of the label. The listed pathogens in the labeling were deemed clinically relevant to the indications. *K. aerogenes* was moved to the second list of organisms because there was insufficient clinical experience for this organism. Other discussions included whether

the infections were monomicrobial or polymicrobial, individual patient factors, and the susceptibility profile and molecular characteristics of the isolates.

Nonsusceptibility

The Applicant reported on the emergence of non-susceptibility for the mITT population during clinical studies. This was defined as, "a subject with a pathogen that is susceptible at baseline but is non-susceptible after baseline" [P008MK7625A]. The Applicant used provisional cut-off values for susceptibility to ceftolozane-tazobactam and cut-off values for meropenem susceptibility based on Clinical and Laboratory Standards Institute (CLSI) definitions (M100-S25). The provisional cut-off values for ceftolozane/tazobactam susceptibility were: Enterobacteriaceae ≤4 mcg/mL susceptible, ≥ 8 mcg/mL not susceptible; *P. aeruginosa* ≤8 mcg/mL susceptible, ≥16 mcg/mL not susceptible; Other bacteria ≤8 mcg/mL susceptible, ≥16 mcg/mL not susceptible.

Clinical Microbiology Reviewer's Comment:
It was noted that the definition of emergence of "non-susceptibility" used by the Applicant included isolates with only a 1-dilution change in MIC, which can be sometimes considered within the limits of normal variability for the test, rather than evaluating isolates with ≥2 dilution (4-fold) change in MIC. While at first this may appear a conservative estimate, the Applicant's definition included provisional cut-offs that were above the FDA recognized breakpoint for ceftolozane/tazobactam for Enterobacteriaceae and *P. aeruginosa* by one dilution. A susceptible isolate by this definition would therefore be different than one defined by FDA recognized standards which are currently set as susceptible ≤2 mcg/mL, intermediate 4 mcg/mL, resistant ≥ 8 mcg/mL for Enterobacteriaceae, and susceptible ≤4 mcg/mL, intermediate 8 mcg/mL, resistant ≥ 16 mcg/mL for *P. aeruginosa*. The Applicant's definition of non-susceptible is also different from that of the CLSI in which the term is reserved for isolates that only have a susceptible breakpoint because of the absence or rare occurrence of resistant isolates (CLSI M100).

The Applicant reported that both the TOL/TAZ and meropenem treatment arms had comparable incidences of emergence of resistance, which developed in 29 (12.7%) subjects in the ceftolozane/tazobactam arm compared to 28 (12.0%) subjects in the meropenem arm by the TOC visit. In the ceftolozane/tazobactam treatment arm, the most common pathogens to develop non-susceptibility were 11 *K. pneumoniae* and 8 *A. baumannii* isolates; among *P. aeruginosa* isolates, 3 developed nonsusceptibility.

The Applicant reported that in the meropenem treatment arm, the most common pathogens to develop non-susceptibility were 17 *P. aeruginosa* and 10 *K. pneumoniae* isolates. A lower percentage of subjects with *P. aeruginosa* isolates in the ceftolozane/tazobactam treatment arm (3/63, 4.8%) developed non-susceptibility compared to the meropenem treatment arm (17/65, 26.2%)

Four (4) isolates [*Proteus mirabilis* (2), *K. pneumoniae* (1), and *A. baumannii* (1)] in the ceftolozane/tazobactam treatment arm, and 1 isolate (*A. baumannii*) in the meropenem arm, only had a 1 dilution change in the MIC value after baseline. Even in the case of subjects who had isolates with increased MICs, the Applicant reported clinical and microbiological cure rates of approximately 59% in the ceftolozane tazobactam arm and 54-68% in the meropenem arm at TOC.

Table 78: Emergence of Non-Susceptibility for Baseline Infecting Pathogens (mITT Population)

Category	Statistic	Ceftolozane/ Tazobactam (N=264)	Meropenem (N=247)	% Difference (Meropenem minus Ceftolozane/Tazobactam)
Subjects with a Susceptible Pathogen at Baseline	N1	229	234	
Subjects with Emergence of Non-Susceptible Pathogen(s) by EOT Visit	n (%) Unstratified 95% CI [1]	26 (11.4) (7.87, 16.12)	25 (10.7) (7.34, 15.30)	-0.7 (-6.49, 5.11)
Subjects with Emergence of Non-Susceptible Pathogen(s) by TOC Visit	n (%) Unstratified 95% CI [1]	29 (12.7) (8.96, 17.60)	28 (12.0) (8.41, 16.75)	-0.7 (-6.78, 5.35)

Notes: n=Number of subjects in specific category. N=Number of subjects in mITT population. N1=Number of subjects with a susceptible pathogen at baseline.
Percents are calculated as 100 x (n/N1).
Emergence of non-susceptibility is defined as a subject with a pathogen that is susceptible at baseline, but is non-susceptible after baseline.
Analysis is based on susceptibility data from the central microbiology lab when available. For subjects without central lab susceptibility data at baseline local lab data is used.
[1] The 95% CIs of % difference are unstratified Newcombe CIs. The 95% CIs of each treatment are unstratified Wilson CIs.

Source: [P008MK7625A: analysis-adsl; adms]

Assessment of Superinfecting Pathogens and New Infecting Pathogens
The Applicant used the following definitions for superinfecting pathogen and new infecting pathogen:

- Superinfecting pathogen: an organism other than the baseline pathogen, isolate from a post baseline lower respiratory tract (LRT) specimen obtained in a subject while still on study therapy. Required to meet the following quantitative counts: $\geq 10^5$ CFU/mL for ETA or sputum specimens, $\geq 10^4$ CFU/mL for bronchoalveolar lavage (BAL)/mini-BAL specimen, or $\geq 10^3$ CFU/mL for Phosphate Buffered Saline (PBS) specimen.
- New Infecting Pathogen: an organism other than the causative baseline pathogen, isolated from the LRT culture obtained after the end of study therapy. Required to meet the same criteria listed above.

The table below presents subjects with emergent infections, including a summary of which respiratory pathogens were isolated. Overall, the incidence of emergent infections was comparable in the 2 treatment arms. Superinfections were reported more frequently than new infections in both treatment arms at the TOC visit. The Applicant reported that the incidence of superinfections was 20.5% in the ceftolozane/tazobactam treatment arm and 20.6% in the meropenem treatment arm at TOC. The incidence of new infections was 9.8% and 6.5% of subjects, in the ceftolozane/tazobactam and meropenem treatment arms, respectively.

Clinical Microbiology Reviewer's Comment:
Acinetobacter baumannii was the most common pathogen isolated from subjects with superinfections, while *P. aeruginosa* and *K. pneumoniae* were the most common pathogens isolated from subjects with new infections in both treatment arms.

15.6.4. Interpretive Criteria

Correlation of Broth MICs to Disk Zone Size

Using the error rate bounded method of analysis (Metzler and DaHann) MIC and disk zone diameter correlation was proposed by the Applicant and reevaluated by this reviewer. The bacteria used for the analysis were taken from the Phase 3 HABP/VABP clinical trial. See analysis below:

Clinical Microbiology Reviewer's Comment:
Data provided by the Applicant was displayed in scattergrams (not shown) with zone diameters on the x axis and MICs on the y axis. The error rate-bounded method was used to form a table with the total number of isolates tested and the number of minor, major, or very major discrepancies that were recorded for the isolates. The CLSI guidelines for acceptable discrepancy rates (M23-A4) are below:

Table 79. CLSI Guideline for Acceptable Discrepancy Rates for MIC-Disk Correlation Studies (Without Intermediate Range)

MIC Range	Very Major	Major	Minor
≥R+1	<2%	NA	<5%
R+S	<10%	<10%	<40%
≤ S-1	NA	<2%	<5%

Source: Adapted from CLSI document M23-A4.

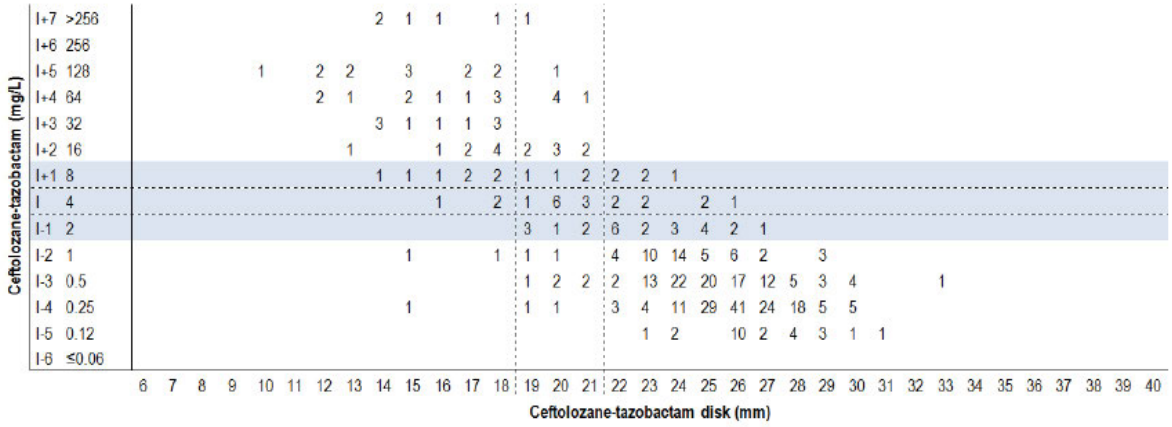
Clinical Microbiology Reviewer's Comment:
The aim of this analysis was to minimize discrepancy rates to best fit within CLSI guidelines. Minimizing error rates is important to prevent negative consequences for patients which could result from errors such as calling strains susceptible when they are known to be resistant.

MIC-Disk Correlations error rates for 128 *P. aeruginosa* were within CLSI guidelines for acceptable discrepancy rates and had low error rates for very major, major and minor categories. Therefore, they were found to be acceptable by this reviewer. The Applicant is not proposing changes to the disk diffusion in comparison to the approved labeling for ceftolozane/tazobactam.

MIC-Disk Correlations for 437 Enterobacteriaceae including ESBL-producing isolates

The Applicant's proposed analysis is below:

Figure 10. Discrepancy Rates for MIC-Disk Correlation for Enterobacteriaceae Using an MIC Susceptible Breakpoint of ≤2 mcg/mL and a Susceptible Zone Diameter Breakpoint of ≥ 22 mm



Source: [Ref. 5.4: 0524SL]

Table 80. M23 Error Rates for Enterobacteriaceae

MIC range	Number	Very major (%)	Major (%)	Minor (%)
≥I+2	58	0	N/A	14 (24.14)
I+1 to I-1	60	5 (8.33)	0	20 (33.33)
≤I-2	319	N/A	3 (0.94)	9 (2.82)
Total	437	5 (1.14)	3 (0.69)	43 (9.84)

Shading represents values greater than the acceptable discrepancy rates from CLSI M23

Source: [Ref. 5.4: 0524SL].

Clinical Microbiology Reviewer's Comment:
The discrepancy rates for the disk diffusion breakpoints proposed by the Applicant are within CLSI guidelines with the exception of the minor error rate in the MIC range ≥I+2. The Applicant's discrepancy rate is at 24.14%, while the recommended rate is ≤5% by CLSI. This is in the minor error category and not a major or very major category. Some isolates which would be classified as resistant by MIC breakpoints will be intermediate by disk diffusion breakpoints. In both cases, a physician might consider whether to choose/recommend a different treatment option. The disk breakpoints were reevaluated by this reviewer to determine if there is any better correlation with MIC values that can be achieved. This reviewer determined that the minor error rates in the MIC range ≥I+2 could not be reduced without introducing very major errors. The Applicant's proposed zone diameter breakpoints for Enterobacteriaceae are 1 mm higher than the current FDA-recognized zone diameter breakpoints, as the Applicant reported that correlation analysis of MICs to zone diameters from PN008 did not support the current FDA-

recognized zone diameter breakpoints. The Applicant reported that the MIC-disk correlation was problematic for Enterobacteriaceae because of *K. pneumoniae* isolates with intermediate zone diameters of 18-21 mm and a wide range of MIC values from 0.5 to >256 mcg/mL.

No disk diffusion breakpoints were proposed by the Applicant or this reviewer for *H. influenzae.* For *H. influenzae*, favorable clinical and microbiological response rates in Study PN008 were noted at the Applicant's proposed breakpoint of MIC ≤0.5 mcg/mL in combination with low MICs to ceftolozane/tazobactam in vitro. The Applicant's proposed breakpoint was accepted.

Susceptibility test interpretive criteria for ceftolozane/tazobactam
Proposed Interpretive Criteria for HABP/VABP indication

The Applicant and this reviewer considered the totality of the data in determining the proposed breakpoints including the following:

- MIC frequency distributions for surveillance and clinical trial isolates of the target
- Bacterial species
- Clinical pharmacology analysis and recommendations
- Efficacy in hollow fiber experiments and in vivo mouse models
- Phase 3 clinical trial data demonstrating efficacy of ceftolozane/tazobactam against the indicated pathogens.

The Applicant's proposed breakpoints for ceftolozane/tazobactam for the new indication of HABP/VABP are shown in the table below:

Table 81. Applicant's Proposed Interpretive Criteria for MIC and Zone Diameter Testing With Ceftolozane/Tazobactam

	MIC (µg/mL)			Zone Diameter (mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2/4	4/4	≥8/4	≥22	19-21	≤18
P. aeruginosa	≤4/4	8/4	≥16/4	≥21	17-20	≤16
H. influenzae (LRT isolates)	≤0.5/4	-	-	-	-	-
S=susceptible, I=intermediate, R=resistant, LRT=lower respiratory tract						

Source: This submission.

Clinical Microbiology Reviewer's Comment:
The currently approved breakpoints for ceftolozane/tazobactam in relation to the organisms in the proposal above are as follows:
CLSI M100 is recognized by FDA for Enterobacteriaceae S|I|R MIC breakpoints of ≤2/4|4/4|≥8/4 mcg/mL and zone diameter breakpoints S|I R of ≥21|18-20|≤17 mm (based on dosage regimen of 1.5 every 8 hours). For *P. aeruginosa* CLSI M100 is recognized by FDA for

MIC breakpoints ≤4/4|8/4|≥16/4 mcg/mL and zone diameter breakpoints of ≥21|17-20|≤16 mm (based on dosage regimen of 1.5 every 8 hours).
The breakpoints proposed by the Applicant were based on the totality of the in vitro, in vivo, clinical and PK/PD data. The data provided by the Applicant was re-evaluated by Clinical Microbiology and other disciplines. The Clinical Microbiology perspective is summarized below.

Clinical Microbiology Reviewer's Comment:
The Applicant and the Agency used the probability of target attainment overlaid with the MIC distributions to assess target attainment for *P. aeruginosa*, Enterobacteriaceae and *H. influenzae*. The Agency's Clinical Pharmacology review team considered the PK-PD target attainment by MIC for adequacy and the PTA was found to support the Applicant's and the Agency's proposals for breakpoints. Likely, the pharmacokinetics could support MIC values as high as 8 mcg/mL, however, there was lack of clinical efficacy at 8 mcg/mL. See also Clinical Pharmacology review for additional information.

Final Clinical Microbiology Recommendations are below:

Final Clinical Microbiology Recommendations

From a Clinical Microbiology perspective, the information provided by the Applicant supports the efficacy of ceftolozane/tazobactam for the treatment of susceptible bacteria for the indication of HABP/VABP. It is recommended that a statement be included with the breakpoints to indicate the appropriate dosing regimen that is to be used. Susceptibility testing interpretive criteria for ceftolozane/tazobactam were proposed by the Applicant and accepted, including MIC breakpoints for *H. influenzae* for the indication of HABP/VABP. The following is a summary of the Agency's proposed Clinical Microbiology labeling changes and rationale:

- Subsection 12.4 has been updated in accordance with the FDA documents titled, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation: Guidance for Industry" and "Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs: Guidance for Industry".
- The first and second lists of organisms were evaluated according to relevance to the indication, and sufficient number of organisms. *K. aerogenes* was (b) (4) placed in the second list due to lack of clinical information.
- Susceptibility interpretive criteria by MIC were reevaluated based on the Applicant's data including surveillance data, animal models, evaluation of PK/PD, and clinical outcome. The Agency's breakpoint decisions for the organism groups listed below were based on the clinical outcome and were supported by PK/PD data.
- Susceptibility interpretive criteria by disk diffusion were reevaluated to define zone diameter ranges that correlated with MIC values, and in an attempt to achieve

acceptable levels of very major, major, and minor errors in the test interpretation. New disk diffusion criteria were proposed by the Applicant for Enterobacteriaceae and accepted by the Agency.

- (b) (4)

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH WANG
05/31/2019 12:14:09 PM

SUMATHI NAMBIAR
05/31/2019 01:01:21 PM
I agree with the review team's assessment and recommendations.

NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 206829/S-008
Priority or Standard	Priority
Submit Date(s)	December 3, 2018
Received Date(s)	December 3, 2018
PDUFA Goal Date	June 3, 2019
Medical Division/Office	Division of Anti-Infective Products/Office of Antimicrobial Products
Review Completion Date	See DARRTS electronic signature page
Established/Proper Name	ceftolozane/tazobactam
Trade Name	ZERBAXA
Pharmacologic Class	Cephalosporin plus Beta-lactamase inhibitor
Applicant	Merck and Co., Inc., on behalf of Cubist Pharmaceuticals, LLC
Dosage form	Intravenous
Applicant proposed Dosing Regimen	3 g every 8 hours (two vials of 1.5 g every 8 hours)
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Indication(s)/Population(s) (if applicable)	Treatment of hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP)

The Office of Biostatistics review of NDA 206829/S-008 is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. My recommendation for this application is approval.

Statistics Reviewer: Cheryl Dixon, Ph.D.
Division of Biometrics IV

Concurring Reviewer: Karen Higgins, Sc.D.
Team Leader
Division of Biometrics IV

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/s/

CHERYL A DIXON
05/31/2019 02:22:22 PM

KAREN M HIGGINS
05/31/2019 02:25:06 PM
I concur.

Clinical Inspection Summary

Date	April 25, 2019
From	Aisha Johnson, MD, MPH, MBA, Medical Officer Min Lu, MD, Acting Team Leader Kassa Ayalew, MD, MPH, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Maria Allende, MD, PhD, Medical Officer Peter Kim, MD, Clinical Team Leader Deborah Wang, Pharm D, Regulatory Project Manager
NDA/BLA #	206829/S008
Applicant	Cubist Pharmaceuticals, LLC, a subsidiary of Merck & Co.
Drug	Ceftazolane/tazobactam (ZERBAXA) FDC
NME (Yes/No)	No
Therapeutic Classification	Antibacterial- Systemic
Proposed Indication(s)	(b) (4)
Consultation Request Date	08 January 2019
Summary Goal Date	03 May 2019
Action Goal Date	03 June 2019
PDUFA Date	03 June 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single Phase 3 study (Protocol CXZ-NP-11-04 (PN008) were submitted as the primary efficacy and safety study in support of this 505(b)(1) supplemental NDA for ceftazolanae/tazobactam (ZERBAXA®). Two study sites (Drs. Ülo Kivistik and Jiri Vyhnal) were selected for clinical inspection as part of PDUFA pre-approval clinical investigation and data validation.

The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indication.

The final compliance classification for Dr. Jiri Vyhnal's site is no action indicated (NAI). The preliminary regulatory compliance classification for Dr. Ülo Kivistik's site is NAI.

A clinical inspection summary addendum will be generated if conclusions change upon receipt and review of the final Establishment Inspection Reports (EIRs). Preliminary classification is based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity.

II. BACKGROUND

ZERBAXA® (ceftolozane/tazobactam (TOL/TAZ), MK-7625A). TOL/TAZ is a fixed dose combination of TOL (an antipseudomonal cephalosporin antibiotic) and TAZ (a β-lactamase inhibitor). TOL/TAZ is currently approved in more than 60 countries for the treatment of complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI). The approved dose for both indications is 1.5 g every 8 hours by IV infusion over one hour in patients 18 years of age and older.

The current NDA proposes to expand the indications for TOL/TAZ to include treatment of nosocomial pneumonia (NP), including ventilator-associated bacterial pneumonia (VABP or VAP). Nosocomial pneumonia (NP) is a hospital-acquired infection that includes hospital-acquired bacterial pneumonia (HABP or HAP) and ventilator-associated bacterial pneumonia (VABP or VAP). HABP is pneumonia diagnosed in a patient after being hospitalized for more than 48 hours or within 7 days after discharge from a hospital. VABP is HABP occurring in a patient already on mechanical ventilation for a minimum of 48 hours. The proposed dose is 3 g (2g TOL/ 1 g TAZ) every 8 hours by IV infusion over one hour for 8-14 days in patients 18 years and older. TOL/TAZ has received Qualified Infectious Disease Product and Fast Track designations for this indication.

A single study, Phase 3 efficacy and safety study using TOL/TAZ for the proposed new indication--Study CXZ-NP-11-04 (PN008), forms the basis for the regulatory decision-making for this application

Protocol CXZ-NP-11-04 (PN008)
A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia

The primary objective of this study was to demonstrate the non-inferiority of ceftolozane/tazobactam versus meropenem in adult subjects with ventilated nosocomial pneumonia (VNP) based on the difference in Day 28 all-cause mortality rates in the intent-to-treat (ITT) population using a non-inferiority margin of 10%.

Patients were randomized in a 1:1 ratio to receive the following:

- Ceftolozane/tazobactam 3g (2g ceftolozane/tazobactam 1 g) every 8 hours IV infusion delivered over 60 ±10 minutes
- Meropenem 1g every 8 hours IV infusion over 60 ±10 minutes

The primary efficacy endpoint was Day 28 all-cause mortality in the ITT population.

A total of 726 subjects were enrolled and to receive TOL/TAZ (362 subjects) or meropenem (364 subjects). This multicenter study was conducted at 119 centers in 29 countries (Australia, Japan, New Zealand, Philippines, South Korea, Taiwan, Croatia, Czech Republic, Estonia, Georgia, Hungary, Latvia, Russia, Serbia, Ukraine, Brazil, Colombia, Guatemala, Israel, Lebanon, South Africa, Belgium, France, Germany, Ireland, Italy, Portugal, Spain, and the United States).

The first subject enrolled in the study on 21 June 2015. The last subject completed the study on 06 June 2018.

Rationale for Site Selection

The clinical sites for inspection were chosen using the Clinical Investigator Site Selection Tool.

Site 23001 was chosen due to its relatively large number of subjects (n=48) and the low mortality rate seen this site (when compared to the study mean).

Site 22007 was chosen due to its relatively large number of subjects (n=35), low mortality for subjects in the ZERBAXA arm, and an imbalance in randomization of VAP and HAP subjects seen between treatment arms.

III. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Dr. Ülo Kivistik North Estonian Medical Centre Foundation, Sütiste tee 19, Tallinn, Harjumaa 13419 Estonia	Site # 23001 Protocol CXA-NP-11-04 (PN008) 48 subjects	March 8-18, 2019	NAI*
Dr. Jiri Vyhnal, Strazovska 1247, Nemocnice Kyjov, p.o. Kyjov, 697 33 Czech Republic	Site # 22007 Protocol CXA-NP-11-04 (PN008) 35 subjects	April 8-11, 2019	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Ülo Kivistik / Site # 23001/ Protocol CXA-NP-11-04 (PN008)

At this site, there were 53 subjects screened, 48 subjects enrolled and randomized. Of these, 44 subjects completed the study. Eleven subject records were reviewed in full. An additional 14 subject records were reviewed for adverse events (AEs). And 30 subject records were reviewed for primary and secondary endpoint data.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

One item was discussed with the clinical investigator during the close out meeting—missing concomitant medication data. For subject (b) (6), diclofenac and pipercuronium bromide were not recorded as concomitant medications.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

OSI Reviewer Comment: Misrepresentation of subject concomitant medications does not appear to be a widespread practice at this site and is therefore unlikely to affect the overall safety and efficacy conclusions of the study data derived from this site.

2. Dr. Jiri Vyhnal/ Site # 22007/ Protocol CXA-NP-11-04 (PN008)

At this site, there were 39 subjects screened and 35 subjects enrolled. A total of 25 subjects completed the study. Ten subjects (seven meropenem subjects, three ceftazolane/tazobactam subjects) discontinued from the study. Informed consent documents for 35 enrolled subjects were reviewed. An audit was conducted for 18 of 35 enrolled subjects for protocol compliance and data listing verification.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

At the end of this inspection, the following finding was discussed with the clinical investigator:

Subject (b) (6) received 1500 mg every 8 hours of ceftolozane/tazobactam instead of 750 mg every 8 hours as outlined in the protocol for patients with a creatinine clearance of 15-29 mL/min. The patient received the incorrect dose for Study Day 1. The dose was corrected for Study Day 2.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued.

OSI Reviewer Comment: The issue of incorrect dosing was corrected immediately and was observed in only a single patient. This practice does not appear to be widespread and in this instance was corrected promptly; therefore, it is unlikely to affect the overall safety and efficacy conclusions of the study data derived from this site. This protocol deviation was included in the study report.

{See appended electronic signature page}

Aisha P. Johnson, M.D, M.P.H, M.B.A
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D.
Acting Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/Sumathi Nambiar
Review Division /Medical Team Leader/Peter Kim
Review Division /Project Manager/Deborah Wang
Review Division/MO/ Maria Allende
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Min Lu
OSI/DCCE/GCP Reviewer/ Aisha Johnson
OSI/ GCP Program Analysts/ Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters

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MIN LU
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KASSA AYALEW
04/25/2019 10:46:42 AM

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA

NDA #:	NDA 206829
Supplement #:	8
Related IND #:	IND 104490
Product Name:	Zerbaxa (ceftolozane/tazobactam)
Indication(s):	(b) (4)
Applicant:	Merck & Co, Inc.
Dates:	Submit Date: December 3, 2018 Filing Date: January 24, 2019 PDUFA Date: June 3, 2019
Review Priority:	Priority
Biometrics Division:	Biometrics IV
Statistical Reviewer:	Cheryl Dixon, Ph.D.
Concurring Reviewers:	Karen Higgins, Sc.D., Team Leader
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Maria Allende, MD Clinical Reviewer Peter Kim, MD Clinical Team Leader
Project Manager:	Deborah Wang, RPh, PharmD

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

This is a supplemental NDA for Zerbaxa. Zerbaxa is a fixed dose combination of ceftolozane (an antipseudomonal cephalosporin antibiotic) and tazobactam (a β lactamase inhibitor). It is currently approved for the treatment of complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI). The proposed indication of this efficacy supplement is the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP). The intended dose is 3 g (2 g ceftolozane/ 1 g tazobactam) every 8 hours by intravenous infusion over 1 hour for 8-14 days. This is twice the currently approved dose for the treatment of cIAI and cUTI.

Zerbaxa received Qualified Infectious Disease Product (QIDP) for a hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia (HABP/VABP) indication on February 2, 2013. Therefore, the supplement qualifies for a priority review.

Primary evidence of efficacy is based on a single Phase 3 study, PN008. PN008 was a randomized double blind multicenter trial of ceftolozane/ tazobactam (TOL/TAZ) vs meropenem in adult subjects with ventilated nosocomial pneumonia (including VABP and ventilated HABP).

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
PN008	MC, R, DB, AC, NI Phase 3 trial	TOL/TAZ /362 meropenem/ 364	Primary: Day 28 all-cause mortality Key Secondary: Clinical cure at TOC	Non-inferiority with respect to Day 28 all-cause mortality and clinical cure at TOC

* MC: multi-center, R: randomized, DB: double-blind, AC: active controlled, NI: non-inferiority TOL/TAZ: ceftolozane/ tazobactam, TOC: test of cure,

2. Assessment of Protocols and Study Reports

The Applicant received substantial input from the FDA, the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA, Japan) on the final study design for Protocol PN008. It was agreed that a single pivotal trial for HABP/VABP would be sufficient provided there was evidence of efficacy and good drug penetration into the epithelial lining fluid was shown. Although meropenem is not approved for nosocomial pneumonia in the United States, it was agreed that it was an appropriate comparator for PN008.

The FDA, EMA, and PMDA required different primary endpoints and statistical analyses to demonstrate non-inferiority. For the FDA, the primary endpoint is all-cause mortality at Day 28. For the EMA and PMDA, the primary endpoint is clinical response at the TOC visit. Therefore, the primary and key secondary efficacy results are presented by regulatory agency in the clinical study report.

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Yes- Interim analysis conducted after 30% of enrolment was completed to evaluate potential safety signals, futility analysis only
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA206829\0085\m5\datasets\p008mk7625a
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADEF1
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation?*	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	Sites requested to be inspected: 22007: high enrollment, lower mortality than study rate in Zerbaxa arm, imbalance in randomization between treatment arms 23001: high enrollment, lower mortality rate than study rate (both treatment arms)
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently	X			

Content Parameter	Yes	No	NA	Comments
documented, and of sufficient quality (e.g., no meaningful data errors).				
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

N/A

5.2. Information Requests/Review Issues

N/A

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/s/

CHERYL A DIXON
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KAREN M HIGGINS
01/28/2019 04:38:49 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	May 22, 2019
Reviewer:	Ronald Wassel, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II)
Team Leader:	Kelly Cao, PharmD DPV II
Subject:	ZERBAXA® (ceftolozane and tazobactam) for injection safety update
OSE RCM #:	2019-1077

1 INTRODUCTION

The Division of Anti-infective Products (DAIP) is reviewing an efficacy supplemental application for Zerbaxa® (NDA 206829/S-008) with the proposed indication for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP).

Prior to completion of DAIP's Medical Review, the medical officer requested an update to the DPV Postmarket Drug Safety Surveillance Summary for Zerbaxa® completed on November 1, 2018, to determine if there are any new safety signals. The November summary did not identify any new safety signals.

2 METHODS AND MATERIALS

DPV reviewed information from the FDA Adverse Event Reporting System (FAERS) and conducted a disproportionality reporting analysis of FAERS data using Empirica Signal and compared the results to the 2018 Surveillance Summary. To focus the search, we looked in FAERS for Designated Medical Events (DMEs), which are adverse events that are considered serious and may often be caused by exposure to drugs, and for which identification is a priority. We also looked for any new events that "signaled" in Empirica Signal. See Appendix A for a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

2.1 FAERS

DPV searched FAERS with the strategy described in Table 1. We searched for all reports instead of from the date of the last search to determine if there were increasing numbers of reports compared to the previous results.

Table 1. FAERS Search Strategy*	
Date of Search	May 3, 2019
Time Period of Search	All reports through May 2, 2019
Search Type	FAERS Business Intelligence Solution (FBIS) Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient – Ceftolozane sulfate\Tazobactam sodium
MedDRA version	22.0
* See Appendix B for a description of the FAERS database.	

2.2 Data Mining

DPV conducted a disproportionality analysis of FAERS data using Empirica Signal with the strategy described in Table 2.

Table 2. Data Mining Search Strategy*	
Data refresh date	May 19, 2019
Product terms	Product active moieties (PAM) (Ceftolozane And Tazobactam)
Empirica Signal run name	PAM (S) (Product active moieties [PAM], Suspect drugs only)
MedDRA search strategy	All adverse events, retrieved at the MedDRA PT level
EB05	> 2
* See Appendix B for a description of data mining of FAERS using Empirica Signal.	

3 RESULTS

3.1 FAERS

The only changes in the reported DMEs from the 2018 review were an increase in the number of reports for pancytopenia from 3 to 13, and for agranulocytosis from 2 to 7. There was one new report for blindness and one for drug reaction with eosinophila and systemic symptoms (DRESS).

- Pancytopenia

  As with the 2018 review in which the 3 reports of pancytopenia represented one case, the 13 reports in this review still represent that one case. The case was reported from France involving a 43-year-old male with a history of graft versus host disease, respiratory distress, drug allergy, anterograde amnesia, cellulitis, abdominal pain, diarrhea, acute myeloblastic leukemia, tendon disorder, fungal infection, fever, pneumocystosis, cessation of smoking, tendonitis, gastro-esophageal reflux, renal failure acute, pain, epilepsy, stem cell transplant, hypertension arterial, total body radiation therapy, depression, myocarditis, pleuropneumonia, prophylaxis against transplant rejection, major depressive disorder, parenteral nutrition, and migraine. Suspect products included Wellvone (atovaquone), Keppra (levetiracetam), Amlor (amlodipine besilate), ramipril, bisoprolol, Targocid (teicoplanin), Cancidas (caspofungin acetate), Ursolvan (ursodeoxycholic acid), Gaviscon (sodium bicarbonate, alginic acid), magnesium alginate, Smofkabiven (amino acids, electrolytes, lipids and dextrose), Zerbaxa (tazobactam sodium, ceftolozane sulfate), Acupan (nefopam hydrochloride), Ditropan (oxybutynin hydrochloride), amikacin, Spasfon (phloroglucinol, trimethylphloroglucinol), paracetamol, sodium alginate, Cellcept (mycophenolate mofetil), Eupressyl (urapidil), Zyvoxid (linezolid), Neural (ciclosporin), Tienam (imipenem, cilastatin sodium), urapidil, Tiorfan (racecadotril), Bactrim, Cymevan

(ganciclovir sodium), Solu-medrol (methylprednisolone sodium succinate), Zelitrex (valaciclovir hydrochloride), and Eupantol (pantoprazole sodium sesquihydrate).

Reviewer's comment: The patient's underlying medical conditions and multiple medications make the cause of pancytopenia difficult to determine, but offer numerous alternatives to Zerbaxa® as the etiology.

- Agranulocytosis

  The seven reports represent three cases, all from foreign sources.

  - A report from Spain of an 87-year-old male treated with Zerbaxa® for a *Pseudomonas* pneumonia was technically not agranulocytosis as the lowest reported neutrophil count was 1,330 (units not provided; agranulocytosis defined as less than 100 neutrophils per microliter of blood).

  - A report from France of a 79-year-old female treated with Zerbaxa® for a *Pseudomonas* bactermia in which the neutrophil count was already decreasing prior to the start of Zerbaxa®.

  - A report from Portugal of a 71-year-old female treated with Zerbaxa® for a *Pseudomonas* pneumonia. No laboratory data were provided to confirm the diagnosis of agranulocytosis. The case was highly confounded as the patient's medical history included ongoing hematological malignancy, ongoing mature B-cell type acute leukemia, febrile neutropenia, ongoing aplasia, ongoing non-hodgkin's lymphoma metastatic, ongoing HIV-1 infection, neutropenic sepsis, ongoing chemotherapy and ongoing radiotherapy; and concomitant medications included tigecycline, fluconazole, rituximab, metamizole, Bactrim, abacavir/lamivudine, and allopurinol.

- Blindness

  This case from Israel lacked any details such as medical history, concomitant medications, and timelines that would allow for an assessment.

- Drug Reaction with Eosinophilia and Systemic Symptoms

  This case from Spain involved a 71-year-old male who was treated with Zerbaxa® and vancomycin for a *Pseudomonas* infection. Five days after starting therapy, the patient developed DRESS. Both drugs were discontinued and the reaction resolved. Both drugs were restarted and DRESS recurred.

  Reviewer's comment: Causality cannot be determined as the case is confounded by concomitant use of vancomycin, which is labeled for DRESS.

3.2 *DATA MINING*

The new unlabeled terms that appeared in the data mining results included *Pancytopenia* and *Amnesia* (due to the one case described above), and *Multiple organ dysfunction syndrome*.

As Zerbaxa® is used to treat patients for serious infections, including unapproved indications such as sepsis and bacteremia, the underlying infections are generally considered the main contributory factor for multiple organ dysfunction syndrome.

4 REVIEWER'S COMMENTS

A review of FAERS and Empirica Signal data did not identify any new safety signals with Zerbaxa®.

5 APPENDICES

5.1 APPENDIX A. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 21.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Pancytopenia
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatic necrosis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant

System Organ Class	Preferred Terms (MedDRA version 21.0)
Immune system disorders	Anaphylactic reaction
	Anaphylactic shock
Infections and infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

5.2 APPENDIX B. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

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KELLY Y CAO
05/22/2019 03:24:01 PM

MEMO TO FILE, NDA 206829/S008

DATE: 5/8/19
RE: NDA 206829 Zerbaxa
FROM: Kerian Grande Roche, Ph.D.
Microbiologist, DAIP
THROUGH: Avery Goodwin, Ph.D.
Clinical Microbiology Team Leader, DAIP

The clinical microbiology review for NDA 206829/S008 is complete and has been added to the multidisciplinary review and evaluation document (UniReview). This review was based on the information currently in the administrative record. If information subsequently added to the administrative record must be reviewed, the appropriate part(s) of the multidisciplinary review and evaluation document (UniReview) will be updated accordingly.

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KERIAN K GRANDE ROCHE
05/08/2019 04:13:43 PM

AVERY C GOODWIN
05/08/2019 04:57:29 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	March 8, 2019
Reviewer:	Ronald Wassel, PharmD, Safety Evaluator Division of Pharmacovigilance II (DPV II)
Team Leader:	Kelly Cao, PharmD DPV II
Subject:	ZERBAXA® (ceftolozane and tazobactam) for injection and hemorrhage and hepatotoxicity
OSE RCM #:	2019-507

1 INTRODUCTION

On January 16, 2019, this reviewer noted an Information Request sent by the Division of Anti-infective Products (DAIP) to the sponsor of Zerbaxa® related to Merck's efficacy supplemental application (NDA 206829/S-008) with the proposed indication for the treatment of (b) (4)

DAIP's Medical Reviewer noted 5 cases of fatal cerebral hemorrhages in the Zerbaxa® treatment arm compared to 0 in the comparator (meropenem) arm, and a total of 14 cerebral bleedings in the Zerbaxa® arm compared to 4 in the meropenem arm. DAIP requested the sponsor provide a review of these cases by a hematology consultant, especially of risk factors, method of diagnosis used, associated laboratory findings, and adverse events that may help explain the imbalance observed between both treatment arms. In addition, DAIP requested the sponsor review their postmarketing safety database for hemorrhagic events in general and for intracerebral bleedings of any kind. Furthermore, DAIP requested the Division of Pharmacovigilance II (DPV II) review FDA Adverse Event Reporting System (FAERS) for reports of hemorrhagic events.

The Medical Reviewer also noted there were two patients in the Zerbaxa® arm who met the laboratory criteria for Hy's law. However, the Medical Reviewer stated one patient had cirrhosis and there was not much information about the second patient to make a good assessment. Because of these findings, DPV also searched FAERS for reports of hepatoxicity.

2 METHODS AND MATERIALS

DPV searched FAERS with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	January 16, 2019
Time Period of Search	None selected (entire database as of search date)
Search Type	FAERS Business Intelligence Solution (FBIS) Product-Manufacturer Reporting Summary
Product Terms	Product Name – Zerbaxa
MedDRA Search Terms (Version 21.1)	Haemorrhage terms (excl laboratory terms) (SMQ) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) (Narrow)
* See Appendix A for a description of the FAERS database.	

3 RESULTS

FAERS case numbers are provided in Appendix B.

Hemorrhage:

- Five unique cases were identified. Only one case was from the United States. Those cases with an active bleed were on anticoagulant therapy, had other confounding factors, or there was incomplete information to make an assessment.

Hepatotoxicity:

- Four cases were identified (all foreign). All of the cases were confounded and alternative etiologies were more likely.

4 REVIEWER'S COMMENTS

A review of FAERS data did not identify a safety signal with Zerbaxa®-associated hemorrhage or hepatotoxicity.

5 APPENDICES

5.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

5.2 APPENDIX B. FAERS CASE NUMBERS

Hemorrhage cases:

10922579
13058146
14047071
14959725
15160726

Hepatotoxicity cases:

12403712
12412618
12893070
13342480

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RONALD T WASSEL
03/08/2019 10:47:17 AM

KELLY Y CAO
03/08/2019 11:16:20 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829sOrig1s008

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 206829 / S-008**

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	12/3/2018	12/3/2018	12/07/2018	06/03/2019*	05/24/2019
Amendment	PA	05/24/2019	05/24/2019	05/24/2019	06/03/2019*	05/24/2019

* Efficacy supplement with a priority goal date

3. **Provides For From Cover Letter:** Addition of indication for the treatment of (b) (4) (b) (4)

4. **Review #**: 1

5. **Clinical Review Division**: Division of Anti-Infective Products (CDER/OND/OAP/DAIP)

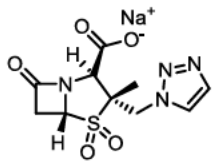
6. **Name and Address of Applicant**:

Cubist Pharmaceuticals LLC Weystrasse 20 Lucerne 6006 Switzerland	**Authorized US Agent:** Merck Sharp & Dohme Corp., *a subsidiary of Merck & Co., Inc.* 1 Merck Drive, P.O. Box 100 Whitehouse Station, NJ 08889-0100

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
ZERBAXA (ceftolozane/tazobactam)	Powder for Injection	1.5 g (1g /0.5g)	Intravenous	Rx	No

8. **ure of Drug Substance**:

(b) (4)	USAN: Ceftolozane sulfate Chemical name: 1H-Pyrazolium, 5-amino-4-[[[(2aminoethyl)amino]carbonyl]amino]-2-[[(6R,7R)-7-[[(2Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, sulfate (1:1) Molecular formula: $C_{23}H_{31}N_{12}O_8S_2$ (b) (4) MW: 764.77
	USAN: Tazobactam Sodium (b) (4) Molecular formula: $C_{10}H_{11}N_4NaO_5S$ MW: 322 (b) (4)

9. **Indication**: Treatment of complicated Intra-abdominal Infections (cUTI), used in combination with metronidazole and Complicated Urinary Tract Infections (cIAI), including Pyelonephritis.

10. **Supporting/Relating Documents**: None

11. **Consults**: None (*OND managed efficacy supplement*)

12. **Executive Summary**:

With this OND managed efficacy supplement, Merck, on behalf of Cubist Pharmaceuticals, proposes to add a new indication for the treatment of (b) (4) (b) (4) (b) (4)

The applicant states that the currently marketed product will be used for the proposed dosage and indication of (b) (4) pneumonia, including VAP. Thus, there are no drug product quality changes associated with this supplement.

The applicant's request for a categorical exclusion from the requirements to prepare an Environmental Assessment (EA) under 21 CFR §25.31(b) may be granted, based on the estimated concentration (EIC) of *<1 ppb* for the drug substances (ceftolozane and tazobactam) at the point of entry into the aquatic environment, and the applicant's statement that to the best of the firm's knowledge, no extraordinary circumstances exist in regards to this action a categorical exclusion from the requirements to prepare an EA. See Assessment section for full details.

The updated prescribing information (PI) provided with this supplement proposes no changes to CMC related sections of Section 11 DESCRIPTION and Section 16 HOW SUPPLIED / STORAGE AND HANDLING. Under Section 3 DOSAGE FORMS AND STRENGTHS and the corresponding Highlights section, the applicant added a statement "For doses above 1.5 g, (b) (4) (b) (4) Subsection 2.3 Preparation of Solutions under Section 2 DOSAGE AND ADMINISTRATION with additional clarification as follows:
"For doses above 1.5 g, reconstitute a second vial in the same manner as the first one, withdraw an appropriate volume (per Table 3), and add to the same infusion bag".

(b) (4)

The applicant incorporated all the suggested revisions and the updated PI is acceptable from a CMC perspective.

There are no container and carton labeling changes associated with this submission.

The addition of the new indication for ZERBAXA and the associated labeling revisions are not expected to impact the quality of the drug product, and therefore, are acceptable from a CMC perspective.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Ramesh Gopalaswamy, Ph.D., CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

David B. Lewis, Ph.D., Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC Assessment

I. Background Information

ZERBAXA (ceftolozane/tazobactam) for injection (NDA-206829, approved 19-DEC-2014) is a combination product consisting of ceftolozane sulfate, a cephalosporin-class antibacterial drug and tazobactam sodium, a beta-lactamase inhibitor.

Zerbaxa is a white to yellow sterile powder consisting of ceftolozane sulfate (1.147 g/vial equivalent to 1 g of ceftolozane) and tazobactam sodium (0.537 g/vial equivalent to 0.5 g of tazobactam) packaged single-use glass vials. The product contains sodium chloride (487 mg/vial) as a stabilizing agent, citric acid (21 mg/vial), and L-arginine (approximately 600 mg/vial) as excipients. The drug product is constituted in the vial with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP and an appropriate volume of the reconstituted solution is then added to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP, prior to administration by intravenous infusion.

Currently, Zerbaxa is indicated for the treatment of complicated intra-abdominal infections (cIAI), used in combination with metronidazole and complicated urinary tract infections (cUTI), including Pyelonephritis.

II. Proposed Changes

Merck & Co, the US agent of the applicant, Cubist Pharmaceuticals LLC, submitted a proposal to add a new indication for the treatment of (b) (4)

(b) (4)

III. Data Submitted to Support the Proposed Changes

There is no Module 3 included with this efficacy supplement submission. In the cover letter of the submission, Merck states that the *currently marketed product will be used for the proposed dosage and indication* of (b) (4) pneumonia, including VAP, and that the current filing does not contain any updates to the Chemistry, Manufacturing and Control (CMC) sections of the dossier. Thus, there are no drug product quality changes associated with this supplement.

Review of Module 1

1.7.1. Priority Review Request: The applicant requested request priority review for this efficacy supplement, based Qualified Infectious Disease Product (QIDP) designation for a hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) indication received for Zerbaxa on 2-FEB-2013. It is noted that this submission is designated for priority review based on QIDP.

1.12.14 Environmental Assessment: The applicant requested a categorical exclusion from the requirements to prepare an Environmental Assessment (EA) under 21 CFR §25.31(b), based on the estimated concentration (EIC) of the drug substances (ceftolozane and tazobactam) at the point of entry into the aquatic environment, which is *shown to be below 1 part per billion*

(ppb). The applicant states that the EIC calculation includes all forms and strengths of the drug substances. The applicant further states that to the best of the firm's knowledge, no extraordinary circumstances exist in regards to this action.

Evaluation: ***Acceptable***

The applicant provided calculation of EIC as follows:

EIC-Aquatic (ppb) = A x B x C x D where,
A = kg/year produced for direct use (active moiety) (maximum projection for the United States in the year 2022), see table below
B = 1 / 2.52E+11 liters per day entering POTWs (from the 2012 Needs Survey)
C = year / 365 days
D = 10^9 µg/kg (conversion factor)

		Ceftolozane	Tazobactam
A	kg/year produced for direct use	8.11E+03	2.21E+03
B	1/liters per day entering POTWs*	3.97E-12	3.97E-12
C	year/365 days	2.74E-03	2.74E-03
D	10^9 ug/kg conversion	1.00E+09	1.00E+09
EIC	ppb	8.83E-02	2.41E-02

*flow value used is 2.517E+11 L/day from 2012 Needs Survey, Report to Congress, accessed at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:27:0:

The calculations in the table above indicate that the EIC of the drug substances, ceftolozane and tazobactam, at the point of entry into the aquatic environment in the year 2022 is expected to be well below the threshold value of 1 ppb. Per Environmental Assessment Guidance, the EIC should be based on or include the highest quantity of the active moiety expected to be produced for direct use in *any of the next five years*. Therefore, based on the EIC (< 1 ppb) and the applicant's statement above that to the best of the firm's knowledge, no extraordinary circumstances exist in regards to this action a categorical exclusion from the requirements to prepare an EA, the request for the categorical exclusion may be granted (Ref: Environmental Assessment Guidance).

(b) (4)

(b) (4)

There are no revisions to other CMC related sections – Section 11 DESCRIPTION and Section 16 HOW SUPPLIED/STORAGE AND HANDLING – of the PI.

The applicant incorporated all the suggested revisions and the updated PI (eCTD 0139; 24-MAY-2019) is acceptable from a CMC perspective.

There are no changes to the container and carton labels associated with this submission.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

Low. The applicant proposes to use the currently approved drug product for the proposed indication. Therefore, the changes proposed in the supplement is not expected to impact the quality of the drug product, ZERBAXA (ceftolozane/tazobactam) for injection.

Ramesh Gopalaswamy

Digitally signed by Ramesh Gopalaswamy
Date: 5/24/2019 02:29:29PM
GUID: 56a003a70000dc95f354c8051d776163

David Lewis

Digitally signed by David Lewis
Date: 5/28/2019 08:57:35AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829sOrig1s008

OTHER REVIEW(S)

MEMO TO FILE:	NDA 206829, ZERBAXA®
GOAL DATE:	6/3/2019
TO:	Deborah Wang, R.Ph., PharmD, vProject Manager, DAIP
FROM:	James Wild, Ph.D., Pharmacology Reviewer, DAIP
THROUGH:	Terry Miller, Ph.D., Supervisory Pharmacology Reviewer, DAIP
RE:	PLLR Labeling Revisions for NDA 206829/S-008

BACKGROUND

The NDA 206829/S-008 efficacy supplement seeks approval for using a higher dose of ZERBAXA® (ceftolozane/tazobactam) for the treatment of nosocomial pneumonia. The doses of ceftolozane/tazobactam in ZERBAXA® previously approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) are 1.0 g ceftolozane and 0.5 g tazobactam administered every 8 hours (3 g ceftolozane and 1.5 g tazobactam per day). The new doses of ceftolozane and tazobactam in ZERBAXA® proposed for the treatment of nosocomial pneumonia are 2 grams ceftolozane and 1 g tazobactam administered every 8 hours (6 g ceftolozane and 3 g tazobactam per day).

When ZERBAXA® was first approved in December 2014, PLLR labels were not yet required. In order to accommodate the current PLLR labeling practices and the new maximum recommended dose of ZERBAXA® for nosochomial pneumonia, the reviewer's suggested PLLR revisions shown below for labeling sections 8.1 and 13 have been applied to the new ZERBAXA® product label.

8.1 Pregnancy

Original 2014 ZERBAXA® Label

Pregnancy Category B.

There are no adequate and well-controlled trials in pregnant women with either ceftolozane or tazobactam. Because animal reproduction studies are not always predictive of human response, ZERBAXA should be used during pregnancy only if the potential benefit outweighs the possible risk.

Embryo-fetal development studies performed with intravenous ceftolozane in mice and rats with doses up to 2000 and 1000 mg/kg/day, respectively, revealed no evidence of harm to the fetus. The mean plasma exposure (AUC) values associated with these doses are approximately 7 (mice) and 4 (rats) times the mean daily human ceftolozane exposure in healthy adults at the clinical dose of 1 gram thrice-daily. It is not known if ceftolozane crosses the placenta in animals.

In a pre-postnatal study in rats, intravenous ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal Day 60 male pups at maternal doses of greater than or equal to 300 mg/kg/day. The plasma exposure (AUC) associated with the NOAEL dose of 100 mg/kg/day in rats is approximately 0.4 fold of the mean daily human ceftolozane exposure in healthy adults at the clinical dose of 1 gram thrice-daily.

In an embryo-fetal study in rats, tazobactam administered intravenously at doses up to 3000 mg/kg/day (approximately 19 times the recommended human dose based on body surface area comparison) produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with fetal toxicity. In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre-postnatal study in rats, tazobactam administered intraperitoneally twice daily at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) produced decreased maternal food consumption and body weight gain at the end of gestation and significantly more stillbirths with a tazobactam dose of 1280 mg/kg/day (approximately 8 times the recommended human dose based on body surface area comparison). No effects on the development, function, learning or fertility of F1 pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. F2-generation fetuses were normal for all doses of tazobactam. The NOAEL for reduced F1 body weights was considered to be 40 mg/kg/day (approximately 0.3 times the recommended human dose based on body surface area comparison).

Sponsor’s Proposed PLLR Revisions

(b) (4)

1 Page Draft Labeling has been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

(b) (4)

Final Label

Risk Summary

There are no data available on ZERBAXA, ceftolozane or tazobactam use in pregnant women to allow assessment of a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal or fetal outcomes (see Data). Neither ceftolozane nor tazobactam produced embryo-fetal toxicity when administered to rodents during the period of organogenesis at ceftolozane doses approximately 3.5 times higher in mice and 2 times higher in rats than the maximum recommended human dose (MRHD) of 2 grams every 8 hours based on plasma AUC comparison or at tazobactam doses approximately 10 times higher in rats than the MRHD of 1 gram every 8 hours based on body surface area comparison. In pre-postnatal studies, where pregnant rats were administered intravenous ceftolozane or intraperitoneal tazobactam in gestation and through the lactation period, ceftolozane was associated with a decrease in auditory startle response in first generation offspring at a dose lower than the MRHD based on AUC comparison, and tazobactam was associated with reduced maternal body weight gain and increased still births at a dose equivalent to approximately 4 times the MRHD and reduced fetal body weights in first generation offspring at a dose approximately equivalent to the MRHD based on body surface area comparison (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

While available studies with multiple cephalosporins cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association of cephalosporin use during pregnancy with major birth defects, miscarriage, or other adverse maternal

or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Ceftolozane

Embryo-fetal development studies were performed in mice administered intravenous ceftolozane at doses of 300, 1000, and 2000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 15) and in rats administered intravenous ceftolozane in doses of 100, 300, and 1000 mg/kg/day during the period of organogenesis (Gestation Day 6 through 17). In mice ceftolozane was not associated with maternal or embryo-fetal toxicity with doses up to the highest dose of 2000 mg/kg/day (approximately 3.5 times the MRHD of 2 grams every 8 hours based on plasma AUC comparison). In rats, no embryo-fetal toxicity was observed, but maternal body weight gain was reduced at a ceftolozane dose of 1000 mg/kg/day. No adverse maternal effects in rats were observed at a dose of 300 mg/kg/day and no adverse embryo-fetal effects were observed at a dose of 1000 mg/kg/day (respectively equivalent to approximately 0.7-and 2-times the MRHD based on plasma AUC comparison).

In a pre-postnatal study in rats, intravenous ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal day 60 male pups at maternal doses greater than or equal to 300 mg/kg/day. No adverse effects were observed in rats at a dose of 100 mg/kg/day, a dose lower than the MRHD of 2 grams every 8 hours based on plasma AUC comparison.

Tazobactam

In an embryo-fetal study in rats, tazobactam was administered intravenously during the period of organogenesis (Gestation Day 7 through 17) at doses of 125, 500, and 3000 mg/kg/day. The high dose of 3000 mg/kg/day produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with fetal toxicity. No adverse maternal effects were observed at a dose of 500 mg/kg/day and no adverse fetal effects were observed at a dose of 3000 mg/kg/day (respectively equivalent to approximately 2-and 10-times the MRHD of 1 gram every 8 hours based on body surface area comparison). In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre-postnatal study in rats, tazobactam administered intraperitoneally in doses of 40, 320, and 1280 mg/kg/day at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) was associated with decreased maternal food

consumption and body weight gain at the end of gestation and significantly more stillbirths at the high dose of 1280 mg/kg/day. No effects on the physical development, neurological function, or fertility and reproductive ability of first generation (F1) pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. The second generation (F2) fetuses were normal for all doses of tazobactam. No adverse effects on maternal reproduction were observed at doses up to 320 mg/kg/day and F1 body weights were not reduced at a dose of 40 mg/kg/day (respectively equivalent to approximately 1.0 and 0.1 times the MRHD of 1 gram every 8 hours based on body surface area comparison).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Original 2014 ZERBAXA® Label

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an in vitro mouse lymphoma assay and an in vivo rat bone-marrow micronucleus assay. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in an in vitro microbial mutagenicity (Ames) assay, an in vitro chromosomal aberration assay in Chinese hamster lung fibroblast cells, an in vivo mouse micronucleus assay, and an in vivo unscheduled DNA synthesis (UDS) assay. Ceftolozane was positive for mutagenicity in an in vitro mouse lymphoma assay.

Tazobactam was negative for genotoxicity in an in vitro microbial mutagenicity (Ames) assay, an in vitro chromosomal aberration assay in Chinese hamster lung fibroblast cells, a mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an in vivo rat bone-marrow micronucleus assay, and an in vivo UDS assay. In another mammalian (mouse lymphoma cell) gene-mutation assay, tazobactam was positive for genotoxicity.

Ceftolozane had no adverse effect on fertility in male or female rats at intravenous doses up to 1000 mg/kg/day. The mean plasma exposure (AUC) value at this dose is approximately 3 times the mean daily human ceftolozane exposure value in healthy adults at the clinical dose of 1 gram thrice daily.

In a rat fertility study with intraperitoneal tazobactam twice-daily, male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day

(approximately 4 times the recommended clinical daily dose based on body surface comparison).

Sponsor's Proposed PLLR Revisions

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an *in vitro* mouse lymphoma assay and an *in vivo* rat bone-marrow micronucleus assay. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in the *in vitro* microbial mutagenicity (Ames) assay, the *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, the *in vitro* mouse lymphoma assay, the *in vitro* HPRT assay in Chinese hamster ovary cells, the *in vivo* mouse micronucleus assay, and the *in vivo* unscheduled DNA synthesis (UDS) assay.

Tazobactam was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, a mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an *in vivo* mouse bone-marrow micronucleus assay, and a UDS assay.

(b) (4)

In a rat fertility study with intraperitoneal tazobactam twice-daily, male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 2 times the highest recommended human dose of 1 gram every 8 hours based on body surface comparison).

Final Label

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an *in vitro* mouse lymphoma assay and an *in vivo* rat bone-marrow micronucleus assay. In an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, an *in vitro* mouse lymphoma assay, an *in vitro* HPRT assay in Chinese hamster ovary cells, an *in vivo* mouse micronucleus assay, and an *in vivo* unscheduled DNA synthesis (UDS) assay.

Tazobactam was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells,

an *in vitro* mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an *in vivo* mouse bone-marrow micronucleus assay, and an *in vivo* UDS assay.

Ceftolozane was administered in a fertility study at intravenous doses of 100, 300, and 1000 mg/kg/day to male rats for 28 days before mating and through the mating period and to female rats for 14 days before mating, through the mating period, and until the 7th day of gestation. Ceftolozane had no adverse effect on fertility in male or female rats at doses up to 1000 mg/kg/day (approximately 1.4 times the maximum recommended human dose (MHRD) of 2 grams every 8 hours based on AUC comparison).

In a rat fertility study, intraperitoneal tazobactam doses of 40, 160, and 640 mg/kg/day were administered twice-daily, to male rats beginning 70 days before mating and through the mating period, and to female rats beginning 14 days before mating, during the mating period, and until Gestation Day 21. Male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 2 times the MRHD of 1 gram every 8 hours based on body surface comparison).

RATIONALE FOR CHANGES

Information included in the reviewer's suggested PLLR revisions contributing to the final label includes the administered doses, period of dosing, and nonclinical exposure margins relative to human exposures. The NOAEL doses established in nonclinical developmental and reproductive toxicology studies and the exposure margins relative to the new maximum recommended doses of ceftolozane (CXA-101, FR264205) and tazobactam are shown in Tables 1 and 2 respectively.

Table 1: Summary of NOAEL Values and Exposure Margins Associated with the CXA-101 Developmental and Reproductive Toxicology Studies.

Study	Doses (mg/kg/day)	NOAEL or LOAEL (mg/kg/day)	CXA-101 AUC (mcg·h/mL)	Exposure Margin for a 6000 mg/day Clinical Dose [d,e,f]
CXA-101 Fertility Study in Rats	Male 100, 300, 1000 mg/kg/day	NOAEL = 1000	1584 1604 Mean = 1594[a]	1.6
	Female 100, 300, 1000 mg/kg/day	NOAEL = 1000	1201 1360 Mean = 1281[a]	1.3
CXA-101 Embryo-Fetal Study in Mice	Maternal 300, 1000, 2000 mg/kg/day	NOAEL = 2000	3536[b]	3.5
	Fetus	NOAEL = 2000	3536[b]	3.5
CXA-101 Embryo-Fetal	Maternal 100, 300, 1000	NOAEL = 300	678[c]	0.66

Study in Rats	Fetus	NOAEL = 1000	2013[c]	2.0
CXA-101 Pre-Postnatal Study in Rats	Maternal 100, 300, 1000	NOAEL = 1000	2013[c]	2.0
	F_1	NOAEL =100	230[c]	0.22
		LOAEL = 300 (decreased auditory startle response)	678[c]	0.66
	F_2	NOAEL = 1000	2013[c]	2.0

a Based on the mean Day 28 plasma AUC measurements in Study No.: CXA201-T-001: A 28 Day Intravenous Toxicity Study in Sprague-Dawley Rat, and Study No.: GLR050748: 4-Week Intravenous Dose Toxicokinetic Study of FR264205 in Rats.

b Based on the plasma $AUC_{0\text{-last}}$ measurement for pregnant mice in Study No.: CX.101.TK.002: CB-500,101: A GLP Intravenous Toxicokinetic Study in Pregnant CD-1 Mice.

c Based on the plasma $AUC_{0\text{-24h}}$ measurement for pregnant rats in Study No.: CX.101.TK.001: CB-500,101: A GLP Intravenous Toxicokinetic Study in Pregnant Sprague-Dawley Rats.

d The clinical daily dose of CXA-101 is 2000 mg TID (6000 mg/day) for nosocomial pneumonia. For an average 60 kg human, the daily dose is 100 mg/kg/day.

e The estimated clinical $AUC_{0\text{-24hrs}}$ in pneumonia patients after intravenous administration of 2000 mg CXA-101 TID (6000 mg/day) is 1023 mcg•h/ml.

f All of the exposure margins are based on nonclinical and clinical AUC comparisons.

Table 2: Summary of NOAEL Values and Exposure Margins Associated with the Tazobactam Developmental and Reproductive Toxicology Studies.

Study	Doses (mg/kg/day)	NOAEL or LOAEL (mg/kg/day)	HED[a] (mg/kg/day)	Exposure Margin for a 3000 mg/day Clinical Dose [b,c]
Tazobactam Fertility Study in Rats	Male 40, 160, 640	640	103.2	2.1
	Female 40, 160, 640	640	103.2	2.1
Tazobactam Embryo-Fetal Study in Rats	Maternal 125, 500, and 3000	NOAEL = 500	80.6	1.6
		LOAEL = 3000 (maternal weight loss)	483.9	9.7
	Fetus	3000	483.9	9.7
Tazobactam Pre- Postnatal Study in Rats	Maternal 40, 320, 1280	NOAEL = 320	51.6	1.0
		LOAEL = 1280 (increased still births)	206.5	4.1
	F_1	NOAEL = 40	6.5	0.13
		LOAEL = 320 (reduced fetal body weights)	51.6	1.0

a NOAEL values were divided by 12.3 for mice and 6.2 for rats to determine the human equivalent dose (HED) values based on relative body surface area.

b The clinical daily dose of tazobactam for treatment of nosocomial pneumonia is 1000 mg TID (3000 mg/day). For an average 60 kg human, the daily dose is 50 mg/kg/day.

c All of the exposure margins are based on body surface area comparisons.

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/s/

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09/20/2019 10:40:24 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 2, 2019

To: Maria Allende, M.D.
Division of Anti-Infective Products (DAIP)

Deborah Wang, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use

NDA: 206829/Supplement 008

In response to DAIP's consult request dated January 24, 2019, OPDP has reviewed the proposed product labeling (PI) for Zerbaxa. This supplement (S008) is proposing that Zerbaxa be approved for the treatment of [redacted] (b) (4)

PI: OPDP's comments on the proposed labeling are based on the draft received by electronic mail from DAIP on April 25, 2019, and are provided below.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

27 Pages Draft Labeling have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

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DAVID F FOSS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 19, 2019 **Date consulted:** December 18, 2018

From: Jane Liedtka MD, Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Maria Allende, MD,
Office of Antimicrobial Products (OAP),
Division of Anti-Infective Products (DAIP)

Drug: Zerbaxa (ceftolozane/tazobactam)

NDA: 206829 S-008

Applicant: Cubist Pharmaceuticals, LLC, a subsidiary of Merck and Co., Inc.

Subject: Pregnancy and Lactation Labeling [Priority Review, Efficacy Supplements (ES) and Pregnancy and Lactation Labeling Rule (PLLR) conversion]

Approved Indications: ZERBAXA is a combination product consisting of a cephalosporin-class antibacterial drug and a beta-lactamase inhibitor indicated for the treatment of the following infections caused by designated susceptible microorganisms:

- Complicated Intra-abdominal Infections (cIAIs)used in combination with metronidazole
- Complicated Urinary Tract Infections(cUTI), including Pyelonephritis

Proposed Indication:

- [redacted] - The Zerbaxa dose to be used for this indication, 3 g every 8 hours, is twice the currently approved dose for cUTI and cIAIs (1.5 g every 8 hours)

Materials Reviewed:

- Applicant's submitted background package for NDA 206829 S-008, submitted on December 3, 2018 which contained PLLR
- [redacted],
- DPMH review of Ceftin[3] (cefuroxime axetil) Oral Tablet and Suspension, NDAs 50605, 50672. Jane Liedtka, MD. October 10, 2018. DARRTS Reference ID 4332356.[2]
- DPMH review of Cefoxitin[4], NDA 65214 S-016. Jane Liedtka, MD. January 28, 2019. DARRTS Reference ID 4382168.[2]

INTRODUCTION AND BACKGROUND

On December 3, 2018, the applicant (Cubist Pharmaceuticals) submitted an ES (#S-008) to NDA 206829. The applicant updated the package insert to the PLLR format and proposed an additional indication of VAP. DAIP consulted DPMH on December 18, 2018, to assist with the Pregnancy and Lactation subsections of labeling.

- Zerbaxa (ceftolozane/tazobactam) was originally FDA approved on December 19, 2014. The component, tazobactam, is a penicillinanic acid analog used to inactivate bacterial beta lactamases and was first FDA approved in 1993 as a component of Zosyn (piperacillin/ tazobactam).
- DPMH has recently reviewed three other cephalosporins (reviews dated October 10, 2018, July 11, 2018 and January 28, 2019), Ceftin (cefuroxime), [redacted] and cefoxitin for PLLR conversion. Much of the literature review for this product consisted of studies that looked at cephalosporins as a class and were previously reviewed in these documents.

Current State of the Labeling[5]

- Current labeling for Zerbaxa (NDA 206829) was approved on October 26, 2016 and is in PLR but not PLLR format.
- There are no boxed warnings.

[redacted]

[2] The Ceftin, Cefoxitin and [redacted] reviews were a part of the materials reviewed but were not sources relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for these reviews and that being proposed here, the labeling recommendations in this review are based on DPMH's independent analysis of the underlying data.

[3] DPMH review of CEFTIN (cefuroxime axetil) Oral Tablet and Suspension, NDAs 50605, 50672 Jane Liedtka, MD. October 10, 2018. DARRTS Reference ID 4332356.

[4] DPMH review of Cefoxitin, NDA 65214 S-016. Jane Liedtka, MD. January 28, 2019. DARRTS Reference ID 4382168.

[5] Zerbaxa labeling approved October 26, 2016.

- There is a Contraindication in patients "with known serious hypersensitivity to the components of ZERBAXA (ceftolozane and tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class".
- There are Warnings and Precautions for "Decreased efficacy in patients with baseline Creatinine Clearance of 30 to ≤50 mL/min.", "serious hypersensitivity (anaphylactic) reactions" and "*Clostridium difficile*-associated diarrhea" (CDAD).
- There are no interactions with hormonal contraceptives noted in the 2016 label.
- Under "Pregnancy", Cefoxitin is characterized as a Pregnancy Category B drug. The label also states (b) (4)

- Under "Nursing Mothers", the following information is included:

  It is not known whether ceftolozane or tazobactam is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering ZERBAXA to a nursing woman.

REVIEW
PREGNANCY

The reader is referred to DPMH consult review of Ceftin[3], NDA 50605 for discussion of UTI and Pregnancy, background and discussion of some publications from the review of the literature for this product.

Reviewer's Comment
DPMH had recommended inclusion of a "Clinical Considerations" (CC) subheading "Disease-Associated Maternal and/or Embryo/Fetal Risk" (b) (4) *in our Ceftin review which was completed in October of 2018. During the labeling meeting*

for cefoxitin[4], the division advised DPMH that they had decided not to include this CC in either the Ceftin or the cefoxitin label. Their rationale included 1) that they had recently approved another cephalosporin Keflex and had not included this CC in that labeling 2) a belief that any serious infection during pregnancy might have adverse effects on pregnancy outcomes (which I agree may be the case) and 3) that the labeling would become too long if all of the indications were included as CCs since some of their products have multiple indications.

In addition, one of the medical reviewers for DAIP sent me several publications I had not found in my search including a large retrospective cross-sectional study from China that did not show an increase in adverse pregnancy outcomes associated with (b) (4) *pregnancy after controlling for multiple confounders. DPMH will therefore, not include the previously recommended CC for* (b) (4) *in our recommended labeling for this product.*

Nonclinical Experience

See above under Current State of the Labeling

The reader is referred to the full Pharmacology/Toxicology review by James Wild, PhD.

Applicant's Review of Literature

The applicant provided a review of the literature through May 15, 2018 from EMBASE and did not identify any published observational studies that evaluated the use of ceftolozane and tazobactam during pregnancy or lactation.

The reader is referred to DPMH consult review of Ceftin[3], NDA 50605, Cefoxitin[4], N65214 and (b) (4)

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and EMBASE on February 20, 2019 using the search terms "ceftolozane and pregnancy," "ceftolozane and pregnant women," "ceftolozane and pregnancy and birth defects," "ceftolozane and pregnancy and congenital malformations," "ceftolozane and pregnancy and stillbirth," "ceftolozane and spontaneous abortion" and "ceftolozane and pregnancy and miscarriage." No publications specific to ceftolozane were identified that were relevant to use in pregnancy and lactation. Many publications regarding cephalosporins as a class were identified and had previously been discussed in the ceftin[3], cefoxitin[4], and (b) (4) DPMH reviews previously mentioned. The reader is referred to Appendix A of this review for a reproduction of a Table of publications entitled "Cephalosporin Use in Pregnancy: Exposure during the First Trimester" from the ceftin[3] review.

DPMH also conducted a search of published literature in PubMed on February 20, 2019 using the search terms "tazobactam and pregnancy," "tazobactam and pregnant women," "tazobactam and pregnancy and birth defects," "tazobactam and pregnancy and congenital malformations," "tazobactam and pregnancy and stillbirth," "tazobactam and spontaneous abortion" and "tazobactam and pregnancy and miscarriage."

A single publication regarding tazobactam use in pregnancy was identified and is summarized below.

- Bourget[6] et al reported on the "Influence of pregnancy on the pharmacokinetic behavior and the transplacental transfer of the piperacillin-tazobactam (PPR-TZB) combination" which were studied in six patients. Whenever possible, the trans-placental transfer (TPT) of the combination was assessed. The kinetic behavior of both beta-lactams appeared to be identical. Evidence was found during pregnancy of an increase in Vss[7] (50 and 74%) and Cl[8] (64 and 88%) of the combination. The main therapeutic consequence of these events is that maternal circulating levels of PPR-TZB were, by 4 h, less than the MIC[9] of target organisms.

Ceftolozane and tazobactam are not specifically referenced in detail in MicroMedex[10] but the reader is referred to the Beta Lactam discussion for "allergy considerations" to Martindale for other properties and to Shepards for nonclinical data. The authors note that "tazobactam is a Category B medication for all trimesters (TMs).

In Reprotox[10], for tazobactam, the authors "Quick take" states "Based on experimental animal data, tazobactam therapy is not expected to increase the risk of congenital anomalies.

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[11] there is no reference to either Zerbaxa or ceftolozane but the authors state that "in general, cephalosporins are considered compatible in pregnancy". Under tazobactam, the authors' pregnancy summary states "Limited Human Data—Animal Data Suggest Low Risk" and goes on to state

> …there is substantial experience with penicillins in human pregnancy that has shown this class of anti-infectives to be safe for the embryo-fetus. Because tazobactam is a derivative of the penicillin nucleus, it also probably is safe in pregnancy.

Review of Pharmacovigilance Database

Collectively, female worldwide cumulative patient exposure for ceftolozane and tazobactam (ZERBAXA®) is estimated to be 138,013 patient-treatment-days or 378 patient-treatment-years.

According to the applicant, "a cumulative search of the worldwide company database identified a total of 1 spontaneous, prospective pregnancy exposure report and no non-interventional reports". No details, such as maternal age, timing of exposure, etc., were available for this case. The outcome was reported as "pending".

Regarding lactation and "fertility disorders", "no reports were identified from either post-marketing or clinical trial sources".

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[6] Bourget P et al. Influence of pregnancy on the pharmacokinetic behavior and the transplacental transfer of the piperacillin-tazobactam combination. Eur J Obstet Gynecol Reprod Biol. 1998 Jan; 76(1):21-7.
[7] Vss is the apparent volume of distribution at plateau
[8] Cl is the total clearance
[9] MIC is the minimal inhibitory concentration
[10] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 2/20/19.
[11] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

LACTATION

Nonclinical Experience
There are no animal lactation studies for ceftolozane or for tazobactam.

Applicant's Review of Literature
The applicant provided a review of the literature through May 15, 2018 from EMBASE and did not identify any published observational studies that evaluated the use of ceftolozane and tazobactam during pregnancy or lactation.

DPMH's Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[12], Micromedex[10], LactMed[13] and of published literature in PubMed and EMBASE using the search terms "ceftolozane and lactation", "ceftolozane and breastfeeding", "tazobactam and lactation" and "tazobactam and breastfeeding." No relevant data were found in published literature.

There is no reference to Zerbaxa or ceftolozane in Hale[12] but tazobactam is discussed under piperacillin and tazobactam. The average mean elimination half-life of piperacillin and tazobactam is ≈ 0.7-1.0 hours.

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*,[11] the authors' note

> Although specific details were lacking, the manufacturer states that tazobactam is excreted into breast milk in low concentrations. This is consistent with its molecular weight (about 322) and low protein binding.

The relevant "Summary of Use" information on ceftolozane/tazobactam in LactMed[22] states

> No information is available on the clinical use of ceftolozane-tazobactam during breastfeeding. No serious adverse effects have been reported for other cephalosporin antibiotics during breastfeeding. Occasionally disruption of the infant's gastrointestinal flora, resulting in diarrhea or thrush have been reported with cephalosporins, but these effects have not been adequately evaluated. Ceftolozane-tazobactam is acceptable in nursing mothers.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

[12] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[13] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/9/18.

Ceftolozane had no adverse effect on fertility in male or female rats at intravenous doses up to 1000 mg/kg/day. The mean plasma exposure (AUC) value at this dose is approximately 3 times the mean daily human ceftolozane exposure value in healthy adults at the clinical dose of 1 gram thrice daily.

In a rat fertility study with intraperitoneal tazobactam twice-daily, male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 4 times the recommended clinical daily dose based on body surface comparison).

The reader is referred to the full Pharmacology/Toxicology review by James Wild, PhD.

Applicant's Review of Literature
No reports were identified regarding ceftolozane and tazobactam and infertility.

DPMH's Review of the Literature
DPMH conducted a search of published literature in PubMed and EMBASE regarding ceftolozane and tazobactam and their effects on fertility and found no relevant literature.

DISCUSSION AND CONCLUSIONS

Pregnancy
There no data available on Zerbaxa use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available nonclinical studies do not suggest concern for adverse fetal outcomes. However, while available studies with multiple cephalosporins cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with cephalosporin use during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Lactation
There are no data on the presence of ceftolozane in human milk, the effects on the breastfed infant, or the effects on milk production. Tazobactam is present in human milk. There are no data on the effects of tazobactam on the breastfed infant, or the effects on milk production. In general, cephalosporins as a class are considered safe for breastfeeding mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cefoxitin and any potential adverse effects on the breastfed infant from cefoxitin or from the underlying maternal condition.

Females and Males of Reproductive Potential
No literature was identified regarding the effect of Zerbaxa on fertility in humans. No adverse effects on fertility were seen in animals. No recommendations for contraception or pregnancy testing are required; therefore, DPMH recommends omitting subsection 8.3 from labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed these recommendations with the division on March 25, 2019. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Zerbaxa (ceftolozane/tazobactam) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There no data available on Zerbaxa or tazobactam use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available data from published prospective cohort studies, case series, and case reports over several decades have not identified an association with cephalosporin use during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes *(see Data)*. Neither ceftolozane nor tazobactam were teratogenic when administered to rodents during the period of organogenesis at ceftolozane plasma exposures (AUC) 2 to 3.5 times higher than the mean daily human exposure at the highest recommended human dose of 2 grams every 8 hours or at tazobactam doses approximately 10 times higher than the highest recommended human dose of 1 gram every 8 hours based on body surface area comparison. *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

While available studies with multiple cephalosporins cannot definitively establish the absence of risk, published data from prospective cohort studies, case series, and case reports over several decades have not identified an association with cephalosporin use during pregnancy, and major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups.

Animal Data

Ceftolozane

Embryo-fetal development studies performed [redacted] (b) (4)

(b) (4)

Tazobactam

In an embryo-fetal study in rats (b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of ceftolozane or tazobactam in human milk, (b) (4)

Appendix A

Table 1: Cephalosporin Use in Pregnancy: Exposure during the First TM

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments
Muanda et al[14] Canada 2017	Prospective cohort study 1998-2008	139,938 live born singletons; 124469 pregnancies not exposed to antibiotics	exposure to antibiotics (including cephalosporins n=1005) during the first TM	No increased risk of major congenital malformation with cephalosporins compared to controls	Malformation diagnosis based on ICD 9 and 10 codes; prescription drug insurance plan used for drug exposure
Muanda FT et al[15] Canada 2017	Nested case-control within Quebec Pregnancy Cohort (1998-2009)	182369 pregnancies that ended with a clinically detected spontaneous abortion; 87020 matched controls	Exposure to antibiotics (including cephalosporins n=682) during pregnancy	No increased risk of spontaneous abortion with cephalosporins compared to controls	Women ages 15-45 on day 1 gestation and on the drug plan for at least a year; spontaneous abortion defined as < 20 weeks' gestation
Czeizel et al.[17] Hungary 2001	Case control Hungarian Case-control Surveillance Study of Congenital Abnormalities 1980-1996	22,865 pregnant women with fetuses or infants with congenital anomalies; 38,151 women with normal infants (controls), 812 women with infants with Down Syndrome (patient	Exposure to cephalosporins (oral and/or IV) Cases were matched by TM of exposure	No increased risk of congenital abnormalities with exposure to cephalosporins compared to either normal infants of patient controls	Includes stillbirths and infant deaths Retrospective reporting of information in >50% of cases

[14]Muanda FT et al. Use of antibiotics during pregnancy and the risk of congenital malformations: a population based cohort study. Br J Clin Pharmacol. 2017; 83(11):2557-2571.
[15] Muanda FR et al. Use of antibiotics during pregnancy and risk of spontaneous abortion. CMAJ. 2017; 189(17):E625-E633.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments
		controls – used to control for recall bias)			
Ailes EC et al[14] US 2016	Population-based case-control National Birth Defects Prevention Study	608 mothers with an infant born with a major birth defect and 231 control mothers	Exposure to antibiotic during first TM for treatment of a urinary tract infection	Increased risk for anorectal atresia/stenosis (6 cases) with cephalosporin use (OR 5.01, 95% CI 1.34-18.78)	Data is retrospective -- phone interviews conducted up to 24 months after delivery
Lin[16] KJ et al US 2012	Population based case-control Sloan Epidemiology Center Birth Defects Study 1994-2008	877 infants and fetuses with cleft lip with/without cleft palate; 471 infants with cleft palate and 6952 controls 1994-2008	First TM exposure to antibiotics	Increased risk of oral clefts with amoxicillin, but not with cephalosporin use during Pregnancy (OR=2.0, 95% CI 1.0-4.1)	Data is retrospective -- phone interviews with 6 months of delivery Includes stillbirths and therapeutic abortions
Berkovitch M[15] et al Israel 2000	Prospective cohort study (pregnancy registry)	109 pregnancies exposed to cefuroxime ; 106 controls exposed to antibiotics known to be nonteratogenic/ embryotoxic	First TM exposure to antibiotics cefuroxime	No significant difference between groups regarding gestational age at birth, prematurity, birth weight, or major malformations.	Relatively small sample size

[16] Lin KJ, et al. Maternal exposure to amoxicillin and the risk of oral clefts. Epidemiology. 2012; 23(5):699-705.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments
Eric M and Sabo A.[17] Serbia 2008	Prospective cohort study	Women who either terminated pregnancy for medical reasons or delivered at an academic center Jan. 1, 2001 – December 31, 2001 (n=392)	Exposure to antibiotics during first (44%), second (21%) or third TM (37.9%) of pregnancy. (cephalosporin antibacterial use n=104)	Three malformations (2.9%) detected in group exposed to cephalosporins -one cyst of choroid plexis (newborn) -one short lingual frenulum (newborn) -one syndactyly of the 2nd and 3rd toe of the left foot	Data collected through patient interview, detailed infant examination for major/minor birth defects by trained pediatricians, and pathophysiologic examination of fetuses by trained pathologists
Crider KS et al[16] US 2009	Population-based, case-control study	13,155 mothers with an infant born with a major birth defect and 4941 control mothers	Exposure to antibiotic during first TM (cephalosporins n=128)	Cephalosporin associated with atrial septal defects (AOR 1.9, 95% CI 1.1-3.2)	Data is retrospective -- phone interviews up to 24 months after delivery Includes stillbirth and therapeutic abortions Confounding by diagnosis

(b) (4)

[17] Eric M and Sabo A. Teratogenicity of antibacterial agents. Coll Anthropol. 2008; 32(3):919-925.

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/s/

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03/25/2019 03:13:46 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 1, 2019
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 206829/S-008
Product Name and Strength:	Zerbaxa (ceftolozane and tazobactam) for Injection, 1.5 grams per vial
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck, Sharp, & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), on behalf of Cubist Pharmaceuticals LLC, a subsidiary of Merck
FDA Received Date:	December 3, 2018
OSE RCM #:	2018-2674
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

Merck submitted an Efficiancy Supplement for Zerbaxa (ceftolozane and tazobactam) for Injection in order to update the proposed indication to include the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP). Thus, Merck submitted labeling to support the new indication of nosocomial pneumonia, including VAP. Subsequently, the Division of Anti-Infective Products (DAIP) requested that we review the proposed prescribing information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C
FDA Adverse Event Reporting System (FAERS)*	D
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION

Our evaluation of the proposed prescribing information did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Zerbaxa that Merck submitted on December 3, 2018.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Zerbaxa</th></tr>
<tr><td>Initial Approval Date</td><td>December 19, 2014</td></tr>
<tr><td>Active Ingredient</td><td>ceftolozane and tazobactam</td></tr>
<tr><td>Indication</td><td>Treatment of the following indications caused by designated susceptible microorganisms:
Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole
Complicated Urinary Tract Infections (cUTI), including Pyelonephritis
(b) (4)</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion</td></tr>
<tr><td>Dosage Form</td><td>For injection</td></tr>
<tr><td>Strength</td><td>1.5 gram (ceftolozane 1 gram and tazobactam 0.5 gram)</td></tr>
<tr><td>Dose and Frequency</td><td>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 (b) (4) pneumonia, every 8 hours by intravenous infusion administered over 1 hour for patients 18 years or older with creatinine clearance (CrCl) greater than 50 mL/min.
Recommended dosage regimens in patients with impaired renal function:
<table>
<tr><th>Estimated CrCl (mL/min)*</th><th>Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis†</th><th>Nosocomial Pneumonia, Including Ventilator-associated Pneumonia†</th></tr>
<tr><td>30 to 50</td><td>ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours</td><td>ZERBAXA 1.5 g (1 g and 0.5 g) intravenously every 8 hours</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>15 to 29</td><td>ZERBAXA 375 mg (250 mg and 125 mg) intravenously every 8 hours</td><td>ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours</td></tr>
<tr><td>End-stage renal disease (ESRD) on hemodialysis (HD)</td><td>A single loading dose of ZERBAXA 750 mg (500 mg and 250 mg) followed by a ZERBAXA 150 mg (100 mg and 50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)</td><td>A single loading dose of ZERBAXA 2.25 g (1.5 g and 0.75 g) followed by a ZERBAXA 450 mg (300 mg and 150 mg) maintenance dose administered every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)</td></tr>
</table>
* CrCl estimated using Cockcroft-Gault formula
† All doses of ZERBAXA are administered over 1 hour.
</td></tr>
<tr><td>How Supplied</td><td>ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied in single-dose vials containing ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium) per vial. Vials are supplied in cartons containing 10 vials.</td></tr>
<tr><td>Storage</td><td>Vials should be stored refrigerated at 2 to 8°C (36 to 46°F) and protected from light.
The reconstituted solution, once diluted, may be stored for 24 hours at room temperature or for 7 days under refrigeration at 2 to 8° C (36 to 46°F).</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 21, 2019, we searched the L:drive and AIMS using the term, Zerbaxa to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified seven previous reviews[a,b,c,d,e,f,g], that we reviewed and determined that the previous reviews identified are not applicable to this current review.

[a] Kapoor, R. Proprietary Name Review for Zerbaxa (ceftolozane and tazobactam) IND 104490. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 21. RCM No.: 2013-2129.

[b] Winiarski, A. . Proprietary Name Review Memo for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAY 28. RCM No.: 2014-17366.

[c] Winiarski, A. Label and Labeling Review for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 07. RCM No.:2014-946.

[d] Sheppard, J. Label and Labeling Review Memo for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 NOV 07. RCM No.:2014-946-1.

[e] Kolejian, S. Medication Error Postmarket Review for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 01. RCM No.: 2015-588.

[f] Kolejian, S. Label and Labeling Memo for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 13. RCM No.: 2015-588.

[g] Kolejian, S. Label and Labeling Memo for Zerbaxa (ceftolozane and tazobactam) NDA 206829. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MAY 18. RCM No.: 2015-588.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

On February 21, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

Table 3. ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Nursing, and Community newsletters
Search Strategy and Terms	Match Exact Word: Zerbaxa

C.2 Results

A search of the term "Zerbaxa" identified 2 safety briefs associated with the label and labeling of Zerbaxa. The first safety brief[h] describes strength confusion, in which pharmacists and pharmacy technicians prepared incorrect doses of the new combination cephalosporin/beta-lactamase inhibitor, Zerbaxa. The preparation of these incorrect doses was contributed to the way the labeling expresses the strength of each individual ingredient, ceftolozane 1 gram and tazobactam 0.5 gram. This strength expression, ceftolozane 1 gram and tazobactam 0.5 gram, is not consistent with other multiple ingredient products, such as Unazyn (ampicillin and sulbactam) or Zosyn (piperacillin and tazobactam), where the total amount of the two drugs is identified on the label as the strength. And therefore, doses of Zerbaxa have been incorrectly prepare based on the amount or ceftolozane alone. The second safety brief[i] describes similar errors, as those reported in the previous Zerbaxa safety brief, involving Avycaz which also lists the components separately (i.e., ceftazidime 2 gram and avibactam 0.5 gram) to express the strength in the labeling.

The issue with Zerbaxa strength confusion, described in the safety briefs, has been addressed with the appropriate labeling changes. On March 9, 2015, Cubist submitted an email notifying DAIP of four medication error reports received involving the strength statement presentation. DMEPA conducted a postmarket safety review of medication errors related to the strength presentation for Zerbaxa.[e] On March 26, 2015, Cubist submitted proposed container labels and carton labeling revising the product strength as 1.5 g (1 g/0.5 g). Concurrently, they also submitted their proposed healthcare provider letter targeting pharmacists and pharmacy

[h] Institute for Safe Medication Practices. Safety briefs: Strength confusion over Zerbaxa. ISMP Med Saf Alert! April 9, 2015; 20(7)1-2.

[i] Institute for Safe Medication Practices. Safety briefs: Avycaz dosing error. ISMP Med Saf Alert! August 13, 2015; 20(16)1-2.

technicians. On May 20, 2015, Cubist submitted a Labeling Supplement providing updated carton and container labeling, as well as a revised package insert, reflecting the total amount of Zerbaxa in each vial (i.e., 1.5 grams). On May 20, 2015, the revised carton and container labeling, as well as the revised package insert, submitted on May 20, 2015, were approved by the Agency.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

D.1 Methods

On February 21, 2019, we searched FAERS using the criteria in the table below and identified 31 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[j] We excluded all 31 cases (individual cases may describe multiple types of medication errors) because they described; prescribing errors involving improper dose, overdose (n=7), incorrect storage of drug (n=3), expired drug product used (n=3), duplicate cases (n=3), wrong drug (n=1), dose omission (n=1), wrong infusion rate (n=1), drug prescribing error (n=1), case did not involve Zerbaxa (n=1), insufficient information provided to determine the type of medication error (n=1), which were not applicable to this review. Additionally, 10 of these 21 cases (FAERS case numbers: 11026496 – FDA received date 04/14/2015, 11026498 – FDA received date 04/14/2015, 11026500 – FDA received date 04/14/2015, 11026501 – FDA received date 04/14/2015, 11050831 – FDA received date 04/20/2015, 11174467 – FDA received date 06/09/2015, 11191915 – FDA received date 06/16/2015, 11192919 FDA – received date 06/16/2015, 11295681 – FDA received date 7/22/2015, and 11498429 – FDA received date 09/11/2015) involved labeling issues describing medication errors such as improper dose preparation errors resulting in overdosage, as well as labeling concerns and confusion due to the strength expression of each individual ingredient, ceftolozane 1 gram and tazobactam 0.5 gram. As previously discussed above in Appendix C, the container labels, carton labeling, and prescribing information have been updated to address these issues and therefore are not applicable to this review of the PI.

Table 4. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Open search – no date limit
Product Name:	Zerbaxa
Product Active Ingredient (PAI):	ceftolozane and tazobactam
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

D.2 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic

[j] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Zerbaxa labels and labeling submitted by Merck on December 3, 2018.

- Prescribing Information available at the following link: \\cdsesub1\evsprod\nda206829\0085\m1\us\01-crt-uspi-mk7625a-iv-nosocomial-pneumonia.doc
- Prescribing Information – Tracked changes version is available at the following link: \\cdsesub1\evsprod\nda206829\0085\m1\us\01-wrm-uspi-mk7625a-iv-nosocomial-pneumonia.doc

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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DEBORAH E MYERS
03/01/2019 12:07:43 PM

OTTO L TOWNSEND
03/01/2019 03:46:13 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829sOrig1s008

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

From: DeBellas, Carmen
Sent: Friday, May 24, 2019 3:49 PM
To: Ting, Lillian S L
Cc: Wang, Deborah; Dillon Parker, Maureen P
Subject: NDA 206829/S008 ZERBAXA label
Attachments: 03-annotated-uspi-mk7625a-iv-nosocomial-pneumonia.docx

Hi Lillian,

Please find Zerbaxa label for your review. You can contact Deborah on Tuesday to discuss future plans for a teleconference.

Have a nice weekend.

Carmen

Carmen DeBellas, PharmD, RPh
Chief Project Management Staff
Division of Anti-infective Products
Office of Antimicrobial Products
Phone - 301-796-1203

21 Pages Draft Labeling have been Withheld in Full as b4 (CCI/TS) Immediately Following this Page

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/s/

CARMEN L DEBELLAS
05/24/2019 04:00:06 PM

From: Ting, Lillian S L <lillian.ting@merck.com>
Sent: Wednesday, May 22, 2019 11:25 AM
To: Wang, Deborah <Deborah.Wang@fda.hhs.gov>
Cc: Dillon Parker, Maureen P <Maureen.DillonParker@fda.hhs.gov>
Subject: RE: NDA 206829/S008 ZERBAXA Labeling Discussion Comments Attached - Please respond by May 24th 9AM

Dear Deborah

I confirm receipt of the labeling comments.
Thank you.
Regards,
Lillian
****

Lillian Ting, PhD
Director, Global Regulatory Affairs, Vaccine & Infectious Disease
Ph: 732-594-7361 (W), lillian.ting@merck.com
Merck Research Laboratories, 126 East Lincoln Avenue, RY34-B1120, Rahway, NJ 07065

From: Wang, Deborah <Deborah.Wang@fda.hhs.gov>
Sent: Wednesday, May 22, 2019 11:09 AM
To: Ting, Lillian S L <lillian.ting@merck.com>
Cc: Dillon Parker, Maureen P <Maureen.DillonParker@fda.hhs.gov>
Subject: NDA 206829/S008 ZERBAXA Labeling Discussion Comments Attached - Please respond by May 24th 9AM
Importance: High

EXTERNAL EMAIL – Use caution with any links or file attachments.
Hi Lillian,

I've attached our labeling edits as a follow-up response to your May 17, 2019 labeling submission. We request your response by **9AM on May 24, 2019** via email communication and a follow up thereafter with an official NDA submission to the file.

Please include a clean MS Word file and a marked-up MS Word file in your resubmission.

As in previous labeling communications, use the format underline = addition of information and ~~strikeout~~ = deletion of information. If you agree with the FDA's changes please accept those revisions. If you disagree with the FDA's revisions, please use tracked changes as described above and please provide your rationale for your revisions in a comment bubble.

Please let me know if you have questions and please **confirm** receipt of this email communication.

Thanks
Deborah

- - - - - -

Deborah Wang, PharmD
Regulatory Project Manager
Division of Anti- Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue
WO Bldg 22, Room 6349
Silver Spring, MD 20903
(301)796- 9053| Deborah.Wang@fda.hhs.gov

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DEBORAH WANG
05/23/2019 09:54:18 AM

NDA 206829/S-008

LABELING DISCUSSION COMMENTS

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Lillian Ting, PhD
Director, Global Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 34-B188
Rahway, NJ 07065-0900

Dear Dr. Ting:

Please refer to your supplemental new drug application (sNDA) dated December 3, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZERBAXA (ceftolozane/tazobactam) for injection.

We also refer to our February 1, 2019, letter in which we notified you of our target date of May 10, 2019, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the *PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2018 Through 2022*.

We have reviewed your December 3, 2018 draft labeling and have proposed revisions that are included as enclosures: Prescribing Information and Exposure Margin Tables as a reference for Sections 8.1 and 13 of the labeling. We request that you resubmit labeling that addresses these issues by May 17, 2019. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- Regulations and related guidance documents

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, call Deborah Wang, PharmD, Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker, MS
Chief, Regulatory Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
- Content of Labeling
  - Prescribing information
- Exposure Margin Tables

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Exposure Margins for Ceftolozane and Tazobactam in Developmental and Reproductive Toxicology Studies

Table 1: Summary of NOAEL Values and Exposure Margins Associated with the CXA-101 Developmental and Reproductive Toxicology Studies.

Study	Doses (mg/kg/day)	LOAEL or NOAEL (mg/kg/day)	CXA-101 AUC (mcg·h/mL)	Exposure Margin for a 6000 mg/day Clinical Dose [d,e,f]
CXA-101 Fertility Study in Rats	Male 100, 300, 1000 mg/kg/day	NOAEL = 1000	1584 1604 Mean = 1594[a]	4.1
	Female 100, 300, 1000 mg/kg/day	NOAEL = 1000	1201 1360 Mean = 1281[a]	3.3
CXA-101 Embryo-Fetal Study in Mice	Maternal 300, 1000, 2000 mg/kg/day	NOAEL = 2000	3536[b]	9.0
	Fetus	NOAEL = 2000	3536[b]	9.0
CXA-101 Embryo-Fetal Study in Rats	Maternal 100, 300, 1000	NOAEL = 300	678[c]	1.7
	Fetus	NOAEL = 1000	2013[c]	5.1
CXA-101 Pre-Postnatal Study in Rats	Maternal 100, 300, 1000	NOAEL = 1000	2013[c]	5.1
	F_1	NOAEL =100	230[c]	0.59
		LOAEL = 300 (decreased auditory startle response)	678[c]	1.7
	F_2	NOAEL = 1000	2013[c]	5.1

[a] Based on the mean Day 28 plasma AUC measurements in Study No.: CXA201-T-001: A 28 Day Intravenous Toxicity Study in Sprague-Dawley Rat, and Study No.: GLR050748: 4-Week Intravenous Dose Toxicokinetic Study of FR264205 in Rats.

[b] Based on the plasma $AUC_{0\text{-last}}$ measurement for pregnant mice in Study No.: CX.101.TK.002: CB-500,101: A GLP Intravenous Toxicokinetic Study in Pregnant CD-1 Mice.

[c] Based on the plasma $AUC_{0\text{-}24h}$ measurement for pregnant rats in Study No.: CX.101.TK.001: CB-500,101: A GLP Intravenous Toxicokinetic Study in Pregnant Sprague-Dawley Rats.

[d] The clinical daily dose of CXA-101 is 2000 mg TID (6000 mg) for nosocomial pneumonia. For an average 60 kg human, the daily dose is 100 mg/kg/day.

[e] The clinical AUC in healthy adults after 10 days of intravenous administration of 1000 mg CXA-101 TID (3000 mg/day) is 182 mcg•h/ml and for 2000 mg/day TID the clinical AUC is 392 mcg•h/ml.

[f] All of the exposure margins are based on nonclinical and clinical AUC comparisons.

Table 2: Summary of NOAEL Values and Exposure Margins Associated with the Tazobactam Developmental and Reproductive Toxicology Studies.

Study	Doses (mg/kg/day)	LOAEL or NOAEL (mg/kg/day)	HED[a] (mg/kg/day)	Exposure Margin for a 3000 mg/day Clinical Dose [b,c]
Tazobactam Fertility Study in Rats	Male 40, 160, 640	NOAEL = 640	103.2	2.1
	Female 40, 160, 640	NOAEL = 640	103.2	2.1
Tazobactam Embryo-Fetal Study in Rats	Maternal 125, 500, and 3000	NOAEL = 500	80.6	1.6
		LOAEL = 3000 (maternal weight loss)	483.9	9.7
	Fetus	3000	483.9	9.7
Tazobactam Pre- Postnatal Study in Rats	Maternal 40, 320, 1280	NOAEL = 320	51.6	1.0
		LOAEL = 1280 (increased still births)	206.5	4.1
	F_1	NOAEL = 40	6.5	0.13
		LOAEL = 320 (reduced fetal body weights)	51.6	1.0

a NOAEL values were divided by 6.2 for rats to determine the human equivalent dose (HED) values based on relative body surface area.

b The clinical daily dose of tazobactam for treatment of is 1000 mg TID (3000 mg/day). For an average 60 kg human, the daily dose is 50 mg/kg/day.

c All of the exposure margins are based on body surface area comparisons.

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/s/

MAUREEN P DILLON PARKER
05/10/2019 06:52:28 PM

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/s/

DEBORAH WANG
04/15/2019 03:21:56 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829/S-008

INFORMATION REQUEST

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Lillian Ting, PhD
Director, Global Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 34-B188
Rahway, NJ 07065-0900

Dear Dr. Ting:

Please refer to your supplemental New Drug Application (sNDA) dated December 3, 2018, received December 3, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zerbaxa (ceftolozane/tazobactam) for injection.

Your original Zerbaxa (ceftolozane/tazobactam) for injection application (NDA 206829) was a 505(b)(2) application that relied upon Zosyn NDA 050684. Your supplement proposes to add a new condition of use to labeling while continuing to rely on the investigations (including investigations not conducted by or for Cubist Pharmaceuticals and for which Cubist Pharmaceuticals does not have a right of reference or use) that supported the previous approval of the Zerbaxa 505(b)(2) NDA. Therefore, your supplement is a 505(b)(2) supplement that relies upon Zosyn NDA 050864.

FDA has explained that "[f]or a 505(b)(2) supplement that seeks approval for a new indication or other condition of use, the 505(b)(2) applicant currently is required to submit an appropriate patent certification or statement for each timely filed patent that claims the listed drug(s) relied upon or a method of using such drug(s) for which the applicant is seeking approval (see section 505(b)(2) of the FD&C Act)" ("Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule," 81 FR 69580, 69617 (October 6, 2016)).

We remind you that if you elect to submit a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(*4*)) with respect to a listed patent, the certification must be accompanied by a statement that you will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(b) with respect to sending the notice and under § 314.52(c) with

respect to the content of the notice. We note that the 45-day period provided for in section 505(c)(3)(C) of the FD&C Act would apply.

If you have any questions, please contact Deborah Wang, PharmD, Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
03/28/2019 03:24:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206829/S-008

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Cubist Pharmaceuticals, LLC
c/o Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Lillian Ting, PhD
Director, Global Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY 34-B188
Rahway, NJ 07065-0900

Dear Dr. Ting:

Please refer to your supplemental New Drug Application (sNDA) dated December 3, 2018, received December 3, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ZERBAXA (ceftolozane and tazobactam) for injection.

We also refer to your amendments dated January 9, 18 and 23, 2019.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 3, 2019.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement and/or commitment requests by May 10, 2019.

We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed prescribing information (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the prescribing information (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Deborah Wang, PharmD, Regulatory Project Manager, at (301)796-9053.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
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