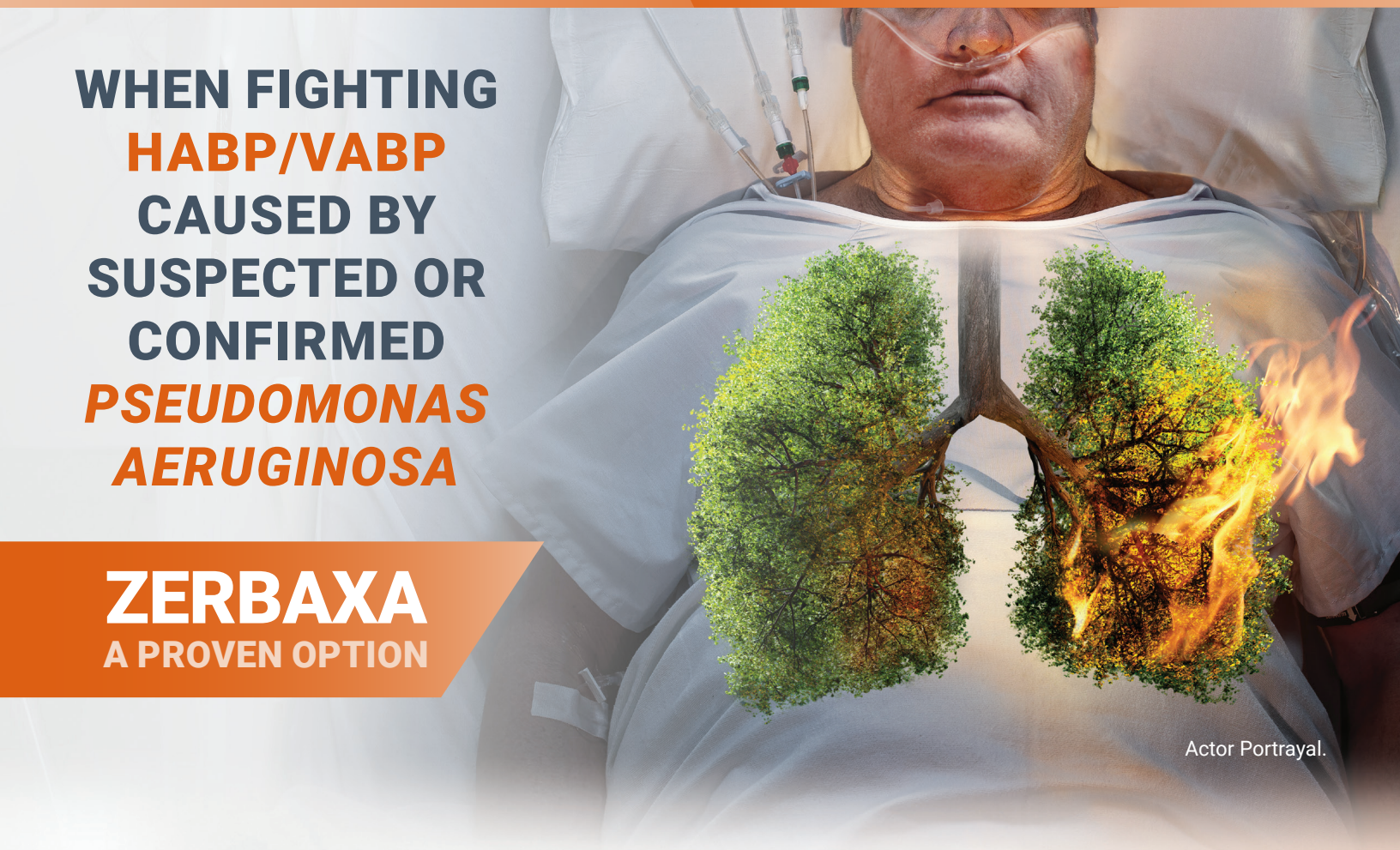
WHEN FIGHTING HABP/VABP CAUSED BY SUSPECTED OR CONFIRMED *PSEUDOMONAS AERUGINOSA*

ZERBAXA
A PROVEN OPTION



Actor Portrayal.

Selected Indication

ZERBAXA is indicated for the treatment of adult patients (18 years and older) with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), 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.*

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.

Important Safety Information

- **Patients with renal impairment:** Dose adjustment is required for adult patients with CrCl 50 mL/min or less. All doses of ZERBAXA are administered over 1 hour. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly.

Please read the additional Important Safety Information on page 4.

ZERBAXA®
ceftolozane and tazobactam
for injection (1.5 g)

According to US SMART Surveillance Data

P. AERUGINOSA INCLUDING THOSE WITH CERTAIN MECHANISMS OF RESISTANCE, IS THE MOST PREVALENT GRAM-NEGATIVE PATHOGEN IN THE ICU[1]

According to data from the SMART (Study for Monitoring Antimicrobial Resistance Trends) Surveillance Program, which collected isolates in 2018, *Pseudomonas aeruginosa* was identified as the most prevalent Gram-negative pathogen in US ICU patients, representing 32% (n = 234) of 731 Gram-negative respiratory isolates.[1]

PATIENTS HOSPITALIZED WITH INFECTIONS CAUSED BY MDR *P. AERUGINOSA* HAD A HIGH MORTALITY RATE, WITH NEARLY 1 IN 4 PATIENTS AFFECTED[2]

Based on a meta-analysis of retrospective data collected from 78 US acute care hospitals during 2013-2015 of consecutive adult patients (N=1904) who were admitted as inpatients with culture-confirmed non-duplicate *P. aeruginosa* infections from a respiratory source. The risk of multidrug-resistance (MDR) was estimated on mortality and other variables.[2]

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SELECT RISK FACTORS FOR INFECTIONS CAUSED BY *P. AERUGINOSA*, INCLUDING THOSE WITH CERTAIN MECHANISMS OF RESISTANCE[3-5]

Prior *P. aeruginosa* infection[4]

Recent antibiotic use/exposure[5]

Hospital readmission <30 days[3]

Use of invasive devices[3]

Admission from LTAC[5]

Prolonged hospitalization[3]

Based on a retrospective case-control study at a single center of patients with *P. aeruginosa* isolates recovered from January 2019 to December 2020.[3] MDR *P. aeruginosa* was defined as non-susceptibility to at least one agent in three or more anti-pseudomonal antimicrobial categories.[3]

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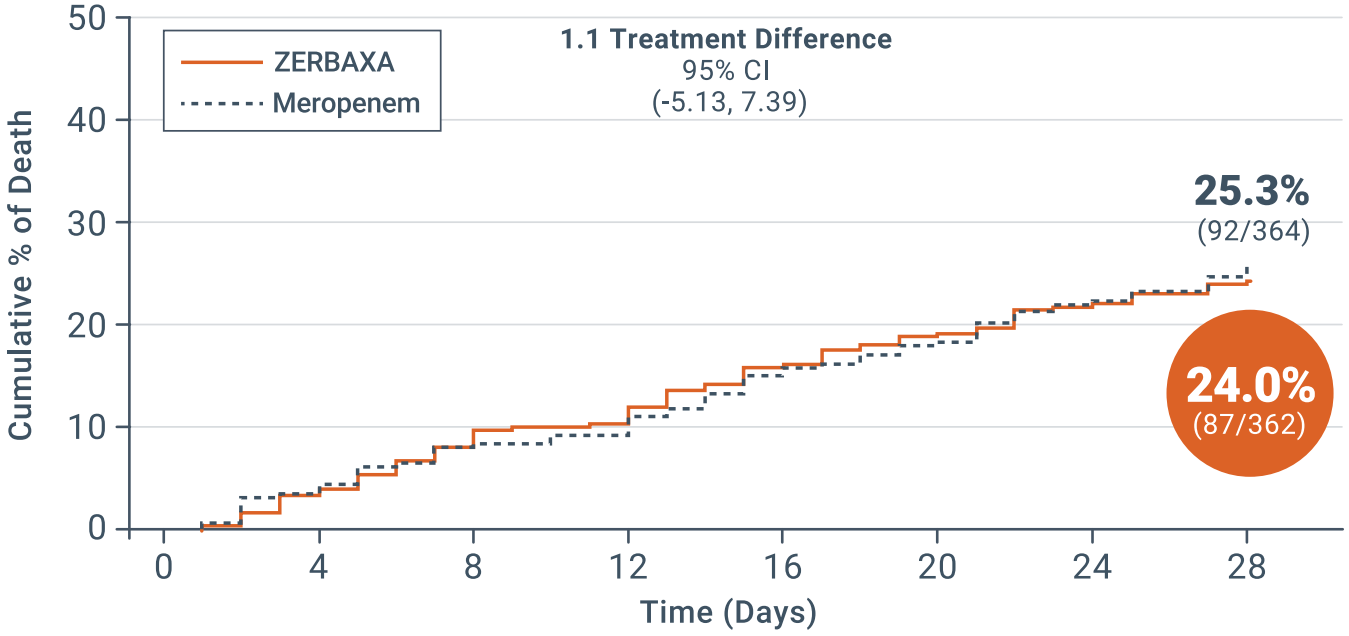
In ASPECT-NP, a phase 3, double-blind, multinational comparator-controlled noninferiority study*

ZERBAXA Achieved Noninferiority in Day 28 All-Cause Mortality vs Meropenem in Adult Patients With HABP/VABP in ITT Population[6]

Primary endpoint: Day 28 all-cause mortality rates were 24% for ZERBAXA vs 25.3% for meropenem, for a treatment difference of 1.1% (95% CI -5.13, 7.39)[6]

Kaplan-Meier, Overall ITT population (N=726)[7,a]



Subject at Risk*

ZER	362	347	325	317	301	289	279	271
MER	364	345	331	321	304	294	280	268

*Number of study patients alive and remaining on study.

[a]The Kaplan-Meier plots were not powered to demonstrate statistical significance in subgroups and individual time points. Subgroup analyses were not designed for noninferiority testing.[6-8]

*__ASPECT-NP:__ A total of 726 adult patients hospitalized with HABP/VABP were enrolled in a phase 3, double-blind, multinational comparator-controlled noninferiority study, comparing ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) intravenously every 8 hours (n=362) to meropenem (1 g) intravenously every 8 hours (n=364) for 8 to 14 days of therapy. All patients had to be intubated and on mechanical ventilation at randomization.[6]

__Primary efficacy endpoint:__ Day 28 all-cause mortality. Objective was to demonstrate the noninferiority of ZERBAXA versus meropenem in adult patients. For analysis of the treatment differences, 95% confidence intervals (CIs) were calculated as stratified Newcombe CIs.[6]

Important Safety Information (*continued*)

- **Hypersensitivity:** ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane/tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials. Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactams. If an anaphylactic reaction to ZERBAXA occurs, discontinue use and institute appropriate therapy.

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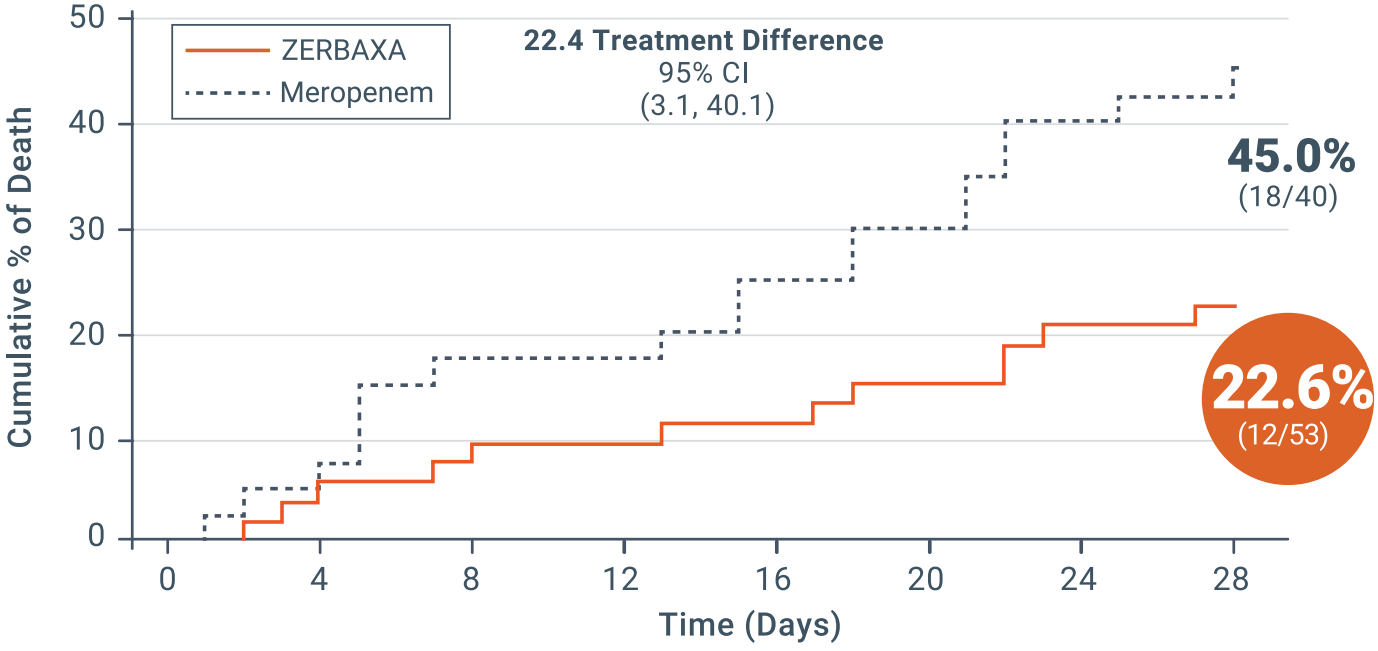
Subgroup of participants who failed prior antibiotic therapy in ASPECT-NP in ITT population[8]

Kaplan-Meier (ITT, Failed Prior Antibiotic Therapy) (N=93)[8,a]



Subject at Risk*

ZER	53	50	48	48	47	45	42	41
MER	40	37	33	33	30	28	24	22

*Number of study patients alive and remaining on study.

[a] Unstratified Newcombe CIs; positive differences are in favor of ceftolozane/tazobactam; negative differences are in favor of meropenem.[8]

The Kaplan-Meier plots were not powered to demonstrate statistical significance in subgroups and individual time points. Subgroup analyses were not designed for noninferiority testing.[6-8]

Additional information and limitations for failed prior antibiotic therapy subgroup with HABP/VABP[8]:

- Participants who were failing prior antibacterial therapy were a prospectively defined subgroup.
- Antibacterial therapy received 72 h prior to starting study treatment in participants who were failing antibacterial treatment before included: beta-lactam/BLI, fluoroquinolones, cephalosporins, aminoglycosides, macrolides, and carbapenems.
- Participants with missing/indeterminate data were reported as deceased.

Important Safety Information (*continued*)

- ***Clostridioides difficile*-associated diarrhea (CDAD),** ranging from mild diarrhea to fatal colitis, has been reported with nearly all systemic antibacterial agents, including ZERBAXA. 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, antibacterial use not directed against *C. difficile* should be discontinued, if possible.

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ZERBAXA is active in vitro in the presence of select key mechanisms of resistance

P. aeruginosa isolates with the most prevalent mechanisms of resistance (AmpC, loss of outer membrane porin, upregulation of efflux pumps) and some ESBLs

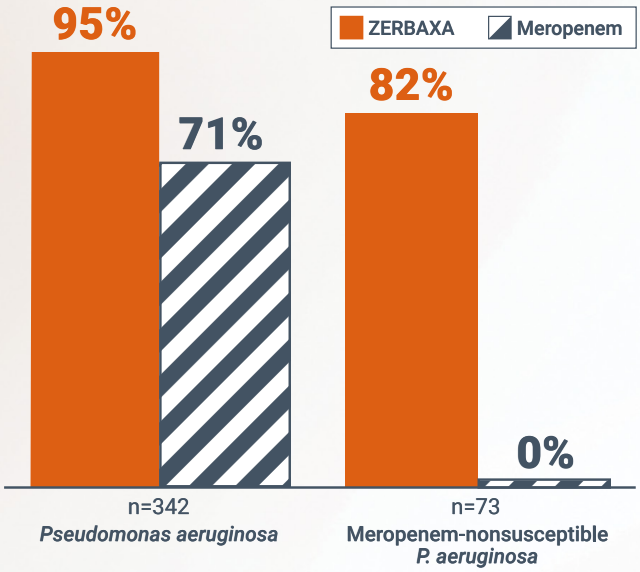
P. aeruginosa isolates			ESBLs			
Chromosomal AmpC	Loss of outer membrane porin[a]	Upregulation of efflux pumps[b]	TEM	SHV	CTX-M	OXA
✓	✓	✓	✓	✓	✓	✓

[a]OprD; [b]MexXY, MexAB.

- **ZERBAXA is not active against bacteria that produce serine carbapenemases (*K. pneumoniae* carbapenemase [KPC]) and metallo-beta-lactamases**

ZERBAXA demonstrated potent in vitro activity

Susceptibility rates for select ICU respiratory tract isolates in US surveillance data (2023-2024)[9,a]



- **The clinical significance of in vitro data is unknown**
- **Limitations of the SMART data include:** Lack of clinical information to confirm nosocomial versus community-acquired isolates, relatively small number of isolates tested each year (n=250 per site), small number of sites, and change of sites participating in SMART study over time
- Culture and susceptibility information and local epidemiology should be considered in modifying antibacterial therapy
- ZERBAXA is not active against bacteria that produce serine carbapenemases (*K. pneumoniae* carbapenemase [KPC]), and metallo-beta-lactamases

[a] Isolates were collected as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART 2023-2024).[9]

Study Design[9]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) represents the commitment of Merck to monitor the in vitro susceptibility of clinical bacterial Gram-negative isolates to antimicrobials in intra-abdominal (since 2002), urinary tract (since 2009), respiratory tract (since 2015), and bloodstream infections (since 2019). SMART was initiated in 2002 and is a global study. This report specifically focuses on isolates from respiratory tract infections (RTIs), collected from 2023 and 2024.

Minimum inhibitory concentration (MIC) values for ceftolozane/tazobactam and comparator agents were determined using the broth microdilution methodology recommended by the Clinical and Laboratory Standards Institute (CLSI) that was current in the year the data was collected. The following breakpoints were used to test for the susceptibility of *P. aeruginosa* for ZERBAXA (MICs [mcg/mL]): ≤4/4 (susceptible).

Important Safety Information (*continued*)

- **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.

Please read the additional Important Safety Information on the next page.

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Demonstrated adverse reactions profile

In ASPECT-NP, the most common adverse reaction (>5%) occurring in patients with HABP/VABP receiving ZERBAXA were hepatic transaminase increased, renal impairment/renal failure, and diarrhea.

Adverse reactions occurring in 2% or greater of adult patients (18 years and older) receiving ZERBAXA in a phase 3 HABP/VABP clinical trial

	HABP/VABP, Including Ventilator-Associated Pneumonia	
	ZERBAXA[a] (N=361) n (%)	Meropenem (N=359) n (%)
Hepatic transaminase increased[b]	43 (11.9)	26 (7.2)
Renal impairment/renal failure[c]	32 (8.9)	22 (6.1)
Diarrhea	23 (6.4)	25 (7.0)
Intracranial hemorrhage[d]	16 (4.4)	5 (1.4)
Vomiting	12 (3.3)	10 (2.8)
Clostridioides difficile colitis[e]	10 (2.8)	2 (0.6)

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

Prescribe ZERBAXA earlier for appropriate patients with HABP/VABP caused by suspected or confirmed *P. aeruginosa*

Important Safety Information (*continued*)

- **Adverse reactions in adult patients with HABP/VABP:** The most common adverse reactions occurring in ≥5% of adult patients receiving ZERBAXA in the HABP/VABP trial were hepatic transaminase increased (11.9%), renal impairment/renal failure (8.9%), and diarrhea (6.4%).

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2024 IDSA Guidance* includes:

- Ceftolozane-tazobactam for the treatment of certain infections caused by MDR *P. aeruginosa* in critically ill patients or patients with poor source control[10,a]
- Ceftolozane-tazobactam for treatment of select polymicrobial infections such as those caused by both ESBL-E and *P. aeruginosa* with certain mechanisms of resistance.[10,a]

*2024 Infectious Diseases Society of America (IDSA) Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections.
[a]Dosing suggestions in IDSA guidance for several agents may differ from dosing in approved labels.

Dosage of ZERBAXA in adult patients with CrCl >50 mL/min

The recommended dose for adult patients with HABP/VABP and CrCl >50 mL/min is 3 g over a 1-hour period every 8 hours for 8 to 14 days.

Renal dosing adjustments for patients with HABP/VABP per estimated CrCl (mL/min)[b,c]:

- **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

For patients with end-stage renal disease on hemodialysis: 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 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).

[b]Creatinine clearance (CrCl) estimated using Cockcroft-Gault formula; [c]All doses of ZERBAXA are administered over 1 hour.

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Before prescribing ZERBAXA, please read the accompanying Prescribing Information. For additional copies of the Prescribing Information, please call 800-672-6372, visit zerbaxa.com, or contact your Merck representative.

References: 1. Moise PA, Gonzalez M, Alekseeva I, et al. *JAC-Antimicrob Resist.* 2021;3(1):dlaa129. doi:10.1093/jacamr/dlaa129 **2.** Tabak YP, Merchant S, Ye G, et al. *JHI.* (2019);103(2):134-141. doi:10.1016/j.jhin.2019.06.005 **3.** Yang AF, Huang V, Samaroo-Campbell J, et al. *IPIP.* 2023;5(3):100296. doi:10.1016/j.infpip.2023.100296 **4.** Reynolds D, Kollef M. *Drugs.* 2021;81(18):2117-2131. **5.** CDC. US Department of Health and Human Services. CRPA Carbapenem-resistant *Pseudomonas aeruginosa.* 2024. **6.** Kollef MH, Nováček M, Kivistik Ü, et al. *Lancet Infect Dis.* 2019;19(12):1299-1311. **7.** Data available on request from the Merck National Service Center via email at daprequests@merck.com. Please specify information package US-ZER-01413. **8.** Kollef MH, Timsit JF, Martin-Loeches I, et al. *Crit Care.* 2022;26(1):373. doi:10.1186/s13054-022-04192-w **9.** Data available on request from the Merck National Service Center via email at daprequests@merck.com. Please specify information package US-ZER-02083. **10.** Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. *Clin Infect Dis.* Published online August 7, 2024. doi:10.1093/cid/ciae403

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