In patients with cIAI...

WHEN THE RESISTANCE RISK IS HIGH,

THE EMPIRIC CHOICE IS CLEAR

XERAVA™
(eravacycline) for injection

Indications and Usage
XERAVA is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, *Clostridium perfringens*, *Bacteroides* species, and *Parabacteroides distasonis* in patients 18 years or older.

Limitations of Use
XERAVA is not indicated for the treatment of complicated urinary tract infections (cUTI).

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

cIAI, complicated intra-abdominal infection.

Active against important resistant pathogens

Provides the appropriate coverage needed in a polymicrobial infection like cIAI[1]

- Covers many Gram-negative, Gram-positive, and anaerobic bacteria relevant to cIAI, including many resistant strains[1]
  - Active against ESBL-producing Enterobacteriaceae, such as *E coli* and *K pneumoniae*,[1] which are identified as high-priority pathogens by the CDC and WHO[2,3]
  - Active against *B fragilis*[1]

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XERAVA and other antibacterial drugs, XERAVA 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.

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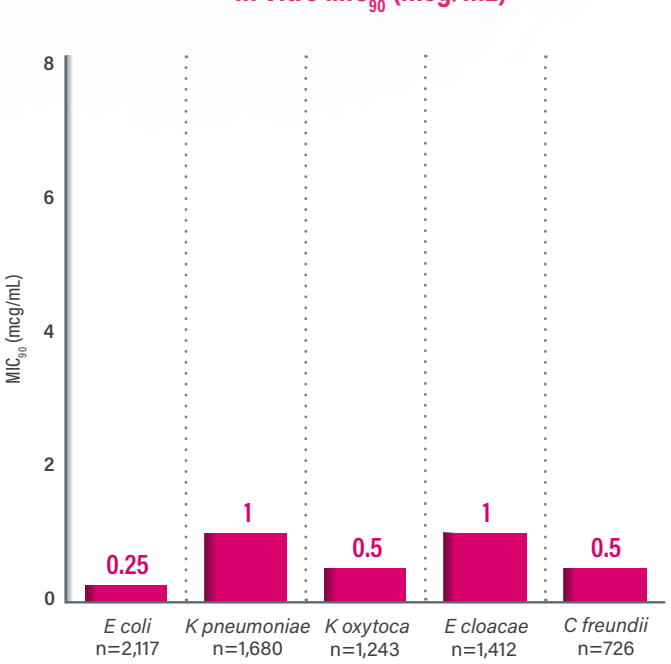
Activity across a range of Gram-negative bacteria that may be encountered in cIAI[4]



In vitro activity does not necessarily correlate with clinical efficacy.

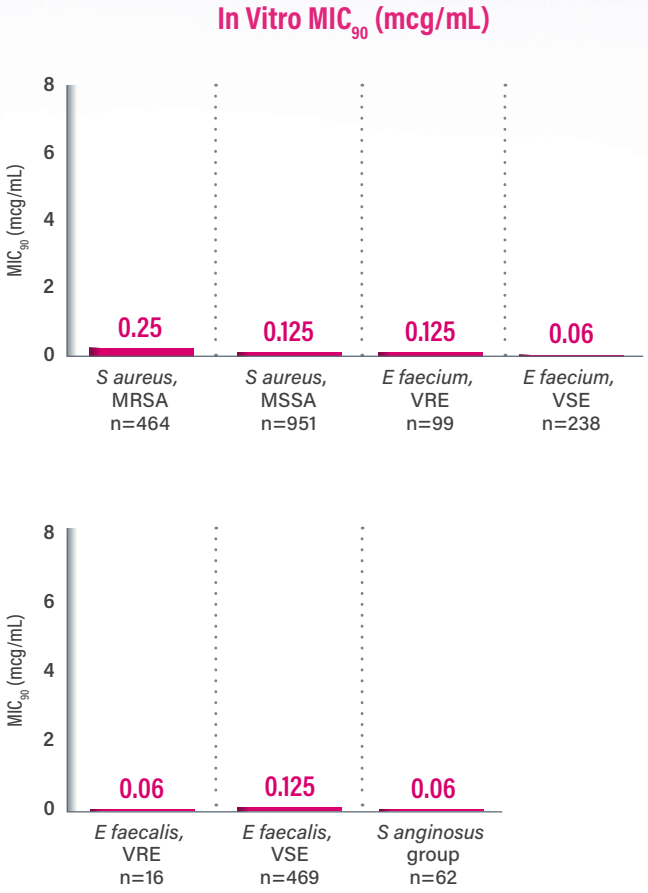
B fragilis, *Bacteroides fragilis*; CDC, Centers for Disease Control and Prevention; *C freundii*, *Citrobacter freundii*; *E cloacae*, *Enterobacter cloacae*; *E coli*, *Escherichia coli*; ESBL, extended-spectrum beta-lactamase; *K oxytoca*, *Klebsiella oxytoca*; *K pneumoniae*, *Klebsiella pneumoniae*; MIC, minimum inhibitory concentration; WHO, World Health Organization.

Important Safety Information

XERAVA is contraindicated for use in patients with known hypersensitivity to eravacycline, tetracycline-class antibacterial drugs, or to any of the excipients. Life-threatening hypersensitivity (anaphylactic) reactions have been reported with XERAVA.

XERAVA™ (eravacycline) for injection

Low MICs against a range of Gram-positive bacteria, including MRSA and VRE[4]



In vitro activity does not necessarily correlate with clinical efficacy.

Important Safety Information (cont'd)

The use of XERAVA during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia.

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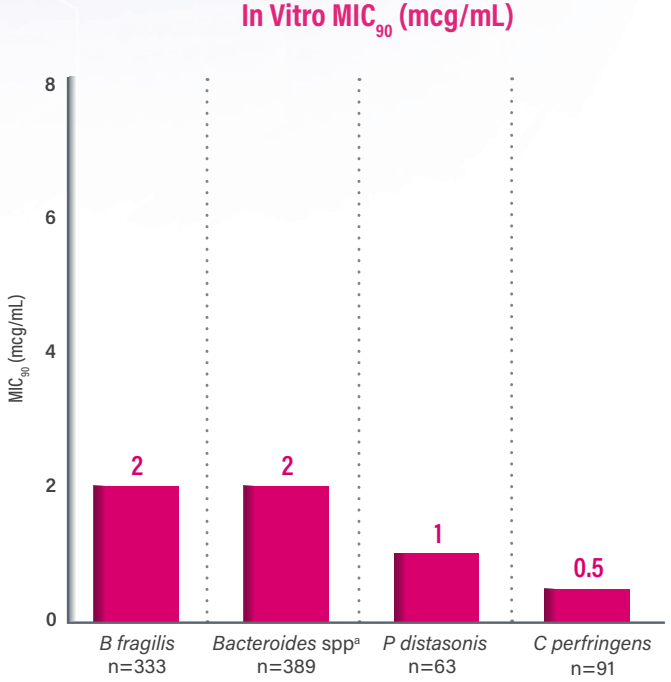
Broad anaerobic activity[4]



[a]Includes *B caccae*, *B ovatus*, *B vulgatus*, *B uniformis*, and *B thetaiotaomicron*.

In vitro activity does not necessarily correlate with clinical efficacy.

B caccae, *Bacteroides caccae*; *B ovatus*, *Bacteroides ovatus*; *B thetaiotaomicron*, *Bacteroides thetaiotaomicron*; *B uniformis*, *Bacteroides uniformis*; *B vulgatus*, *Bacteroides vulgatus*; *C perfringens*, *Clostridium perfringens*; *E faecalis*, *Enterococcus faecalis*; *E faecium*, *Enterococcus faecium*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *P distasonis*, *Parabacteroides distasonis*; *S anginosus*, *Streptococcus anginosus*; *S aureus*, *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

Important Safety Information (cont'd)

The use of XERAVA during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth.

XERAVA™ (eravacycline) for injection

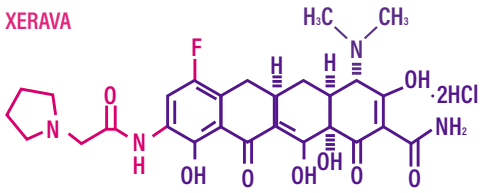
The first fully synthetic fluorocycline antibacterial[1,5]

Key structural modifications to the tetracycline core differentiate XERAVA from other tetracyclines[5]

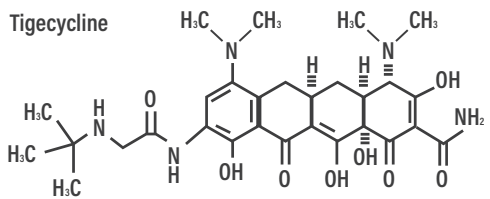
- The C7 and C9 substitutions in eravacycline are not present in any naturally occurring or semisynthetic tetracyclines, and the substitution pattern imparts microbiologic activities, including in vitro activity against Gram-positive and Gram-negative strains expressing certain tetracycline-specific resistance mechanisms[1]
- XERAVA was 2- to 4-fold more potent than tigecycline in vitro against Gram-positive and Gram-negative bacteria, and 2- to 8-fold more potent against most anaerobes[5]
- Low rates of nausea (6.5%), vomiting (3.7%), and diarrhea (2.3%) were among the gastrointestinal-related adverse reactions reported in 2 large clinical trials[1]

Comparison of tetracycline structures[1,6]

XERAVA



Tigecycline



Important Safety Information (cont'd)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis.

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Retains activity against certain tetracycline-specific resistance mechanisms[7]

XERAVA in vitro activity: tetracycline-specific resistance genotypes[7]

	In Vitro MIC (mcg/mL)				
Antibacterial	Control	*tet*(M)	*tet*(K)	*tet*(A)	*tet*(B)
XERAVA	0.063	0.063	0.031	0.25	0.063
Tigecycline	0.063	0.13	0.063	1	0.063
Doxycycline	2	64	4	32	32
Minocycline	0.5	64	1	8	16
Tetracycline	2	128	128	>128	>128
Ceftriaxone	0.063	0.13	0.063	0.13	0.13

Grossman TH, Starosta AL, Fyfe C, et al. *Antimicrob Agents Chemother*. 2012;56(5):2559-2564. Adapted with permission from American Society for Microbiology.

In vitro activity does not necessarily correlate with clinical efficacy.

Important Safety Information (cont'd)

The most common adverse reactions observed in clinical trials (incidence ≥3%) were infusion site reactions (7.7%), nausea (6.5%), and vomiting (3.7%).

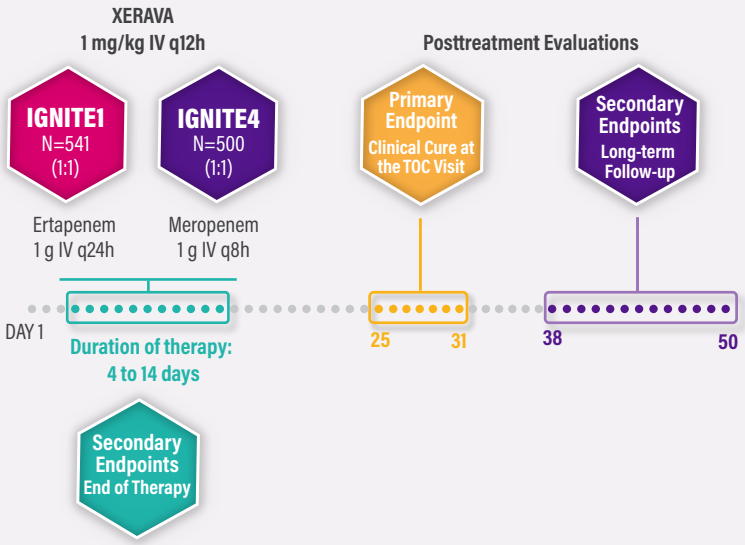
XERAVA™ (eravacycline) for injection

Proven as effective as carbapenems in cIAI[1]

A carbapenem alternative in an age of ESBL-related resistance

- Efficacy demonstrated as monotherapy[1,4,8,9]
- Non-inferior to ertapenem in IGNITE1
- Non-inferior to meropenem in IGNITE4

Study Design: IGNITE1 and IGNITE4[1,8,9]



Primary endpoint: Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection at the TOC visit, which occurred 25 to 31 days after randomization.

IGNITE1: Phase 3, randomized, double-blind, double-dummy, multicenter, prospective study in subjects with cIAI to demonstrate the non-inferiority of XERAVA compared with ertapenem.

IGNITE4: Phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to demonstrate the non-inferiority of XERAVA compared with meropenem in cIAI.

Important Safety Information (cont'd)

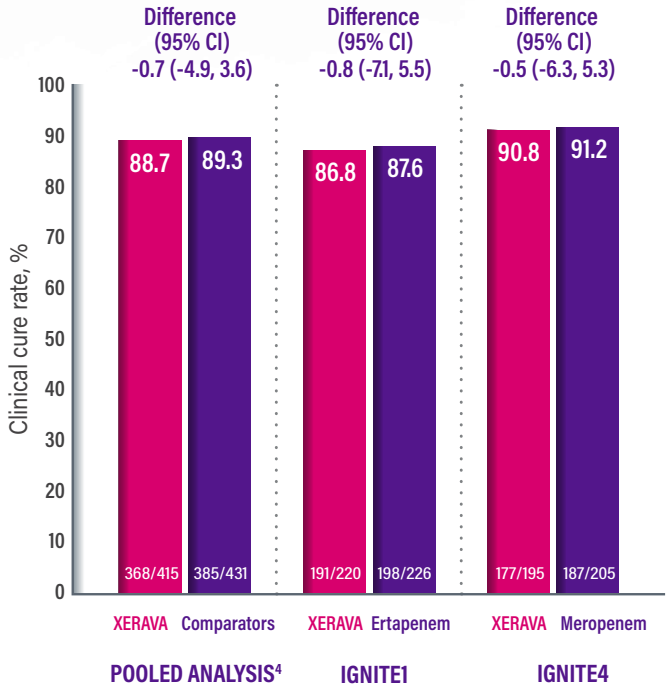
XERAVA is structurally similar to tetracycline-class antibacterial drugs and may have similar adverse reactions. Adverse reactions including photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased BUN, azotemia, acidosis,

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

Efficacy demonstrated in 2 pivotal comparative clinical trials[1]

IGNITE1 + IGNITE4: Primary efficacy endpoint

Clinical response in micro-ITT population at the TOC visit[1,4,8,9]



IV, intravenous; micro-ITT, microbiologic intent-to-treat; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; TOC, Test of Cure.

Important Safety Information (cont'd)

hyperphosphatemia, pancreatitis, and abnormal liver function tests, have been reported for other tetracycline-class antibacterial drugs, and may occur with XERAVA. Discontinue XERAVA if any of these adverse reactions are suspected.

To report SUSPECTED ADVERSE REACTIONS, contact Tetraphase Pharmaceuticals Inc., at 1-833-7-XERAVA (1-833-793-7282) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

XERAVA™
(eravacycline) for injection

Efficacy demonstrated by baseline pathogen

Clinical cure rate at the TOC visit by baseline pathogen[1]

Pooled data from IGNITE1 and IGNITE4

See study design on page 8.

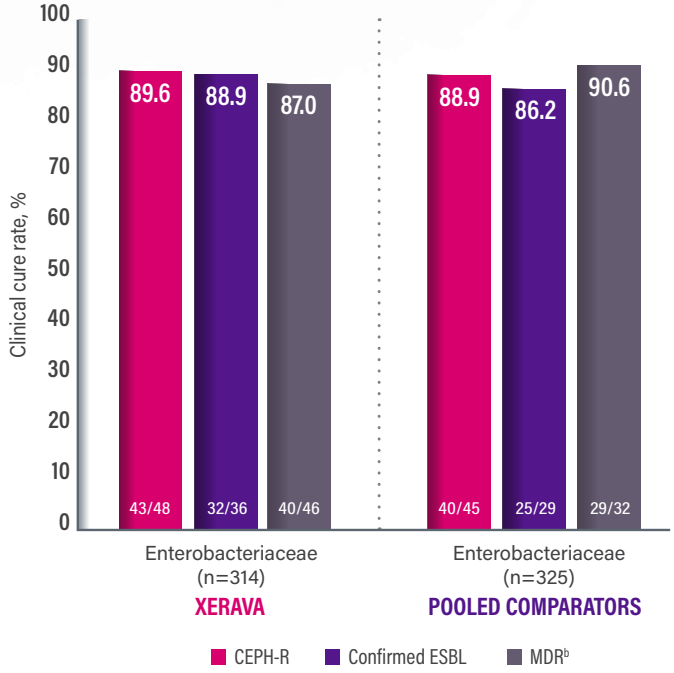
Indications and Usage

XERAVA is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus anginosus* group, *Clostridium perfringens*, *Bacteroides* species, and *Parabacteroides distasonis* in patients 18 years or older.

Clinically effective against challenging resistant bacteria[10]

Clinical cure rate at the TOC visit in Enterobacteriaceae[10]

Pooled data from IGNITE1 and IGNITE4



See study design on page 8.

CEPH-R, cephalosporin-resistant; MDR, multidrug-resistant.

[a]Comparators include ertapenem and meropenem.
[b]MDR pathogens were defined as resistant to at least 1 member of 3 or more antibiotic classes.

Indications and Usage (cont'd)

Limitations of Use

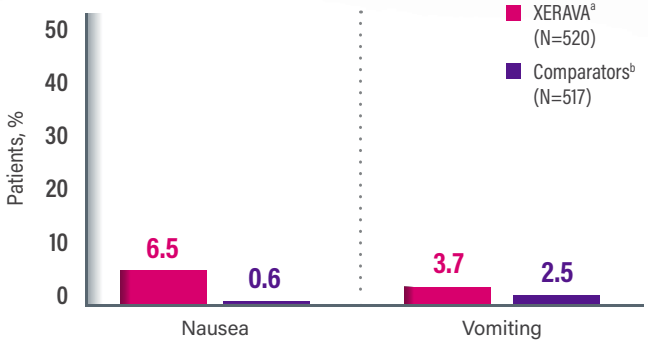
XERAVA is not indicated for the treatment of complicated urinary tract infections (cUTI).

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

Safety profile demonstrated in clinical trials[1]

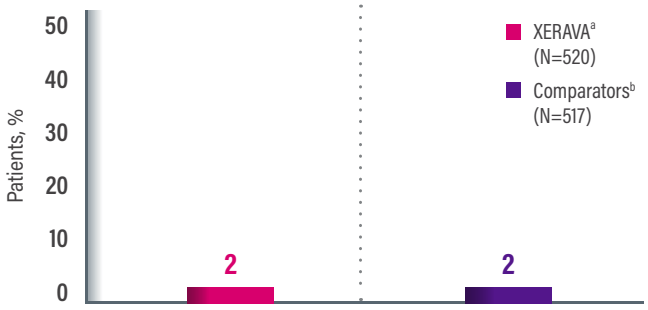
Low rates of nausea and vomiting

Rates of nausea and vomiting reported in patients with cIAI receiving XERAVA in the phase 3 cIAI trials



Low rate of AE-related discontinuation

Rate of discontinuation reported in patients with cIAI receiving XERAVA in controlled clinical studies



The most commonly reported adverse reactions leading to discontinuation of XERAVA were related to gastrointestinal disorders.

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XERAVA and other antibacterial drugs, XERAVA 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.

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

Most common adverse reactions[1]

Adverse reactions reported in ≥3% of patients receiving XERAVA in the phase 3 cIAI trials

Adverse Reactions	XERAVA[a] N=520	Comparators[b] N=517
Infusion site reactions[c]	7.7%	1.9%
Nausea	6.5%	0.6%
Vomiting	3.7%	2.5%

AE, adverse event.

[a]XERAVA dose equals 1 mg/kg every 12 hours IV.
[b]Comparators include ertapenem 1 g every 24 hours IV and meropenem 1 g every 8 hours IV.
[c]Infusion site reactions include catheter/vessel puncture site pain, infusion site extravasation, infusion site hypoaesthesia, infusion/injection site phlebitis, infusion site thrombosis, injection site/vessel puncture site erythema, phlebitis, phlebitis superficial, thrombophlebitis, and vessel puncture site swelling.

Important Safety Information

XERAVA is contraindicated for use in patients with known hypersensitivity to eravacycline, tetracycline-class antibacterial drugs, or to any of the excipients. Life-threatening hypersensitivity (anaphylactic) reactions have been reported with XERAVA.

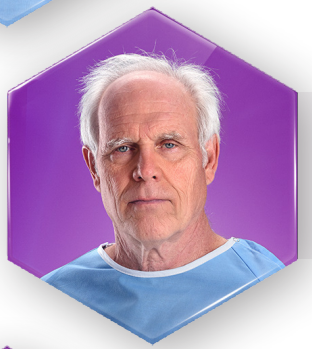
XERAVA™ (eravacycline) for injection

XERAVA: A clear role in the treatment of challenging cases

Patient 1
PENICILLIN ALLERGY

Consider the value of a highly effective, non–beta-lactam antibacterial

- 66-year-old female patient with penicillin allergy
- CT scan revealed perforated appendix
- 60 days post hospitalization and antibiotic treatment for community-acquired pneumonia



Patient 2
LONG-TERM CARE RESIDENT

Consider the value of a highly effective carbapenem alternative

- 79-year-old male patient, long-term care resident
- Small-bowel obstruction with perforation on CT scan
- History of *C difficile*-associated diarrhea
- Renal insufficiency

Patient 3
INTERNATIONAL TRAVELER

Consider the value of a highly effective carbapenem alternative with activity against ESBLs

- 53-year-old female patient
- Recently traveled to an ESBL-endemic area
- Diagnosed with perforated diverticulitis (Hinchey stage IV)
- Received extended-duration oral antibiotics for 2 episodes of acute diverticulitis in the last 3 years, treated in the outpatient setting

C difficile, *Clostridium difficile*; CT, computed tomography.

Important Safety Information (cont'd)

The use of XERAVA during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia.

Important Safety Information (cont'd)

The use of XERAVA during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth.

Patient Cases

Please see additional Important Safety Information throughout and enclosed full Prescribing Information.

XERAVA™ (eravacycline) for injection

Dosage and administration[1]

Weight-based dosing, with no therapeutic drug monitoring required

Dosage and administration for adult patients (≥18 years of age) with cIAI

Administer
1 mg/kg

▼

Every
12 hours
by IV infusion

▼

Over approximately
60 minutes

The recommended duration of treatment is **4 to 14 days**. The duration of therapy should be guided by the severity and location of infection and the patient's clinical response.

Dosage considerations for XERAVA[1]

- No dosage adjustment is necessary in patients with renal impairment
- No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B)
- Adjust XERAVA dosage in patients with severe hepatic impairment (Child Pugh C)
  - Administer XERAVA 1 mg/kg every 12 hours on Day 1 followed by XERAVA 1 mg/kg every 24 hours starting on Day 2 for a total duration of 4 to 14 days
- No dosage adjustment is warranted in patients with concomitant use of a weak or moderate cytochrome P450 isoenzymes (CYP)3A inducer
- Dosage modifications for patients with concomitant use of a strong CYP3A inducer
  - Administer XERAVA 1.5 mg/kg every 12 hours for a total duration of 4 to 14 days

Dosage

Important Safety Information (cont'd)

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis.

Important Safety Information (cont'd)

The most common adverse reactions observed in clinical trials (incidence ≥3%) were infusion site reactions (7.7%), nausea (6.5%), and vomiting (3.7%).

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Storage and handling[1]

Prior to reconstitution, XERAVA should be stored at 2°C to 8°C (36°F–46°F). Keep vial in carton until use.

How supplied[1]

- XERAVA for injection, 50 mg/vial, is a yellow to orange, sterile, preservative-free powder for reconstitution in single-dose 10-mL clear glass vials with a rubber stopper and an aluminum overseal
- Each vial contains 50 mg of eravacycline

Important Safety Information (cont'd)

XERAVA is structurally similar to tetracycline-class antibacterial drugs and may have similar adverse reactions. Adverse reactions including photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased BUN, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver function tests, have been reported for other tetracycline-class antibacterial drugs, and may occur with XERAVA. Discontinue XERAVA if any of these adverse reactions are suspected.

References: 1. XERAVA [prescribing information]. Watertown, MA: Tetraphase Pharmaceuticals, Inc.; 2018. **2.** Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention website. https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed November 27, 2018. **3.** Tacconelli E, Magrini N. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. World Health Organization website. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Accessed November 27, 2018. **4.** Data on file. Watertown, MA: Tetraphase Pharmaceuticals, Inc.; 2018. **5.** Zhanel GG, Cheung D, Adam H, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. *Drugs*. 2016;76(5):567-588. **6.** Tygacil [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; 2018. **7.** Grossman TH, Starosta AL, Fyfe C, et al. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic [published correction appears in *Antimicrob Agents Chemother*. 2015;59(9):5870]. *Antimicrob Agents Chemother*. 2012;56(5):2559-2564. **8.** Solomkin J, Evans D, Slepavicius A, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE 1) trial: a randomized clinical trial. *JAMA Surg*. 2017;152(3):224-232. **9.** Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: results of a phase 3, randomized, multicenter, prospective trial of eravacycline vs meropenem in the treatment of complicated intra-abdominal infections [published online December 18, 2018]. *Clin Infect Dis*. doi:10:1093/cid/ciy1029. **10.** Ditch K, Newman J, Izmailyan S, Fyfe C, Tsai L. Microbiological efficacy of eravacycline against Enterobacteriaceae and *Acinetobacter baumannii*, including MDR isolates: a pooled analysis from IGNITE1 and IGNITE4, two phase 3 trials of complicated intra-abdominal infection. Poster presented at: ASM Microbe; June 7-11, 2018; Atlanta, GA. Poster 629.

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In patients with cIAI...

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The first fully synthetic fluorocycline antibacterial for cIAI[1,5]

- Active against key Gram-negative, Gram-positive, and anaerobic bacteria, including isolates expressing a variety of multidrug resistance mechanisms[1]
- Retains activity against certain tetracycline-specific resistance mechanisms[7]
- Proven as effective as carbapenems in cIAI[1]
- Low rates of nausea (6.5%), vomiting (3.7%), and diarrhea (2.3%) were among the gastrointestinal-related adverse reactions reported in 2 pivotal clinical trials[1]

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LEARN MORE AT XERAVA.COM

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Scan to explore xerava.com

TETRAPHASE PHARMACEUTICALS

XERAVA™ (eravacycline) for injection