

Brand Name: Xerava™

Generic Name: eravacycline

Manufacturer¹: Tetrphase Pharmaceuticals, Inc¹

Drug Class^{1,2,3,4}: Tetracycline antibacterial¹

Uses^{1,2,3,4}:

Labeled Uses: For treatment of complicated intra-abdominal infections in patients 18 years of age and older^{1,2,3,4}.

Unlabeled Uses: None²

Mechanism of Action^{1,2,3,4,5,6,7}:

Eravacycline is a synthetic fluorocycline antibacterial within the tetracycline class of antibacterial drugs. Eravacycline disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit and prevents the incorporation of amino acid residues into elongating peptide chains. Eravacycline has broad spectrum of activity against a variety of Gram-positive, gram-negative and anaerobic bacteria, with the exception of *Pseudomonas aeruginosa*. It is able to overcome common resistance pathways for tetracyclines that include MRSA and carbapenem-resistant Enterobacteriaceae.

Pharmacokinetics^{1,2,3,4}:

Absorption:

T _{max}	Not reported
V _d	321 L
t _½	20 hours
Clearance	Not reported
Protein binding	79% to 90%
Bioavailability	Not applicable

Metabolism: Eravacycline is extensively metabolized in the liver primarily by CYP3A4 and FMO-mediated oxygenation².

Elimination: Eravacycline is primarily excreted through fecal excretion (47%), including 17% as unchanged drug². Eravacycline is also excreted renally 34%, including 20% unchanged.

Efficacy:

Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, Sutcliffe JA, Horn P.
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 Mar 1; 152(3): 224-232

Study Design: Phase III, multicenter, double-blind, active-controlled, parallel design, non-inferiority study.

Description of Study: *Methods:* The study evaluated eravacycline in comparison with ertapenem in patients with complicated intraabdominal infections (cIAI) requiring surgical or percutaneous intervention. Hospitalized patients, were randomized to receive 1.0mg/kg every 24 hours of eravacycline (n = 270) or 1.0mg/kg every 12 hours of ertapenem (n = 271). Both treatments had a minimum of four 24 hour dosing cycles of medication. Evaluation (test-of-cure) of patients occurred at 25 to 31 days post-initiation of study drug, with follow-up visits occurring between 38 to 50 days after first dose. If the lower limit of the 95% CI for the difference in clinical cure rates in the micro-ITT population exceeded -10%, non-inferiority of eravacycline to ertapenem would be declared. Outcomes measured clinical cure, clinical failure or indeterminate/missing results, and these were evaluated at the end of treatment, test of cure, and follow up.

Outcome Results: Clinical cure at the test-of-cure visit were 86.8% in the ervacycline group and 87.6% in the ertapenem group, with the difference in cure rates -0.8% (95% CI, -7.1 to 5.5%). Microbiologically evaluable population also achieved statistical non inferiority, with clinical cure rates of 91.4% (181 of 198) for eravacycline and 95.0% (189 of 199) for ertapenem (difference of -3.6%; 95% CI, -8.9% to 1.5%). There were 9 deaths in the study, 3 among patients receiving eravacycline and 6 among patients receiving ertapenem. The specific causes of death were pulmonary embolism (n = 2), respiratory failure (n = 3), multisystem organ failure (n = 1), cardiac rhythm disturbances (n = 2), and cerebrovascular accident (n = 1). There were more adverse events in the eravacycline treatment group (113) than the ertapenem treatment group (75). The number of severe or life-threatening treatment-emergent adverse events was the same for both groups (n = 13).

Limitations: The study did not account for varying premorbid conditions, clinical details of the acute disease, and perioperative care practices that could have altered outcomes by not being standardized. Further, individual outcome determinants could play a stronger role in patient outcome than selection of antimicrobial agent thus confounding the analysis. Another limitation was that many of the patients were white with 97.4% and 95.9% in the ervacycline and ertapenem groups, respectively which may limit generalizability. This study was sponsored by Tetrphase Pharmaceuticals Inc., manufacturer of eravacycline, who was also involved with the design and conduct of the study. It is difficult to extract generalizability from this study which enrolled patients from 11 countries and who had other baselines differences as a breakdown of which countries the patients were enrolled from and in what numbers was not provided.

Conclusion: Ervacycline was non-inferior to ertapenem in patients with cIAs. The absence of p-values and expressed power make it difficult to fully understand safety and

adverse events, leading to the need for more safety studies to better examine eravacycline's place in therapy.

Solomkin J, Ramesh MK, Sutcliffe JA, et al. Phase 2, Randomized, Double-blind Study of The Efficacy and Safety of Two Dose Regimens of Eravacycline Versus Ertapenem for Adult Community-acquired Complicated Intra-Abdominal Infections. *Antimicrob Agents Chemother.* 2014; 58(4): 1847-1854.

Study Design: Phase II, randomized, multicenter, double-blind, active-controlled, parallel design

Description of Study: *Methods:* The study evaluated the efficacy and safety of two dose regimens of eravacycline compared with ertapenem in adult hospitalized patients with cIAIs. Confirmed cIAI patients requiring surgical or percutaneous intervention and antibacterial therapy were randomized (2:2:1) to receive eravacycline at 1.5 mg/kg of body weight every 24 hours (n = 53), eravacycline at 1.0 mg/kg every 12 hours (n = 56), or ertapenem at 1 g every 24 hours (n = 30) for a minimum of 4 days and a maximum of 14 days. Microbiologically evaluable (ME) patients were evaluated for test-of-cure (TOC) at visit 10 to 14 days after last dose of study drug. *Outcome Results:* Success at TOC for eravacycline at 1.5 mg/kg of body weight every 24 hours was 92.9% (39/42), for eravacycline at 1.0 mg/kg every 12 hours was 100% (41/41), and for the ertapenem group 92.3% (24/26). Treatment emergent adverse effects were 35.8%, 28.6%, and 26.7%, respectively. Both dose regimens of eravacycline were as efficacious as ertapenem in cIAI.

Limitations: The limitations for this study include the inclusion of a high percentage of complicated appendicitis patients (54%). Many patients also had APACHE II scores of <10. Most patients had gram-negative aerobic pathogens (n = 129), with considerable less having gram-positive aerobic pathogens (n = 45) and even fewer still having gram positive anaerobic (n = 6) or gram negative anaerobic pathogens (n = 11) pathogens. This study was sponsored by Tetrphase Pharmaceuticals Inc., manufacturer of eravacycline. Joseph S. Solomkin has received consulting fees from Tetrphase Pharmaceuticals and Joyce A. Sutcliffe, Susannah M. Walpole, and Patrick T. Horn are employees of Tetrphase Pharmaceuticals and authors of this publication.

Conclusion: The study served to support the continued development of eravacycline for the treatment of serious infections, including those caused by drug-resistant Gram-negative pathogens. The absence of p-values and expressed power make it difficult to fully understand safety and adverse events, leading to the need for more safety studies to better examine eravacycline's place in therapy.

Further Studies:

Eravacycline did not achieve co-primary endpoints in complicated urinary tract infections (cUTI) in a phase III clinical trial (IGNITE3), which evaluated the efficacy and safety of once-daily IV eravacycline compared to ertapenem for the treatment of patients with cUTI. The study failed to

meet the co-primary efficacy endpoints of responder rate (a combination of clinical cure and microbiological success) in the microbiological intent-to-treat (micro-ITT) population at the end-of-IV (EOI) treatment visit and at the test-of-cure (TOC) visit, which were evaluated using a 10% non-inferiority margin⁷

Contraindications^{1,2,3,4}:

Hypersensitivity: Known hypersensitivity to eravacycline, tetracycline-class antibacterial drugs, or any of the excipients²

Precautions^{1,2,3,4}:

Dermatologic: Photosensitivity may occur and has been reported with other tetracycline-class antibacterial drugs; discontinue if condition occurs

Endocrine and metabolic: Anti-anabolic action which may lead to increased BUN, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver function tests may occur and has been reported with other tetracycline-class antibacterial drugs; discontinue if conditions occurs

Gastrointestinal: Permanent discoloration of the teeth (yellow-gray-brown) may occur when used during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years); more common during long-term use of the tetracycline-class drugs but has been observed following repeated short-term courses. Enamel hypoplasia may occur and has been reported with tetracycline class drugs. Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, antibacterial drug use not directed against Clostridium difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of Clostridium difficile, and surgical evaluation should be instituted as clinically indicated

Immunologic: Life-threatening hypersensitivity (anaphylactic) reactions have been reported; discontinue use if an allergic reaction occurs. Overgrowth of nonsusceptible organisms, including fungi, may occur; discontinue therapy if such infections occur

Musculoskeletal: Reversible inhibition of bone growth may occur when used during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years; shown to be reversible when therapy discontinued

Neurologic: Pseudotumor cerebri may occur and has been reported with other tetracycline-class antibacterial drugs; discontinue if condition occurs

Special populations: Premature infants are at increased risk for a decrease in fibula growth rate at oral tetracycline doses of 25 mg/kg every 6 hours; reversible upon discontinuation

Adverse Effects^{1,2,3,4}:

Occurring in 1% to 10% of patients

Cardiovascular

Hypotension (1%)

Gastrointestinal

Nausea (7%)

Vomiting (4%)

Diarrhea (2%)

Local

Infusion site reaction (8%)

Miscellaneous

Wound dehiscence (1%)

Occurring in <1% of patients

Postmarketing, and/or case reports: Acute pancreatitis, anaphylaxis, anxiety, chest pain, decreased creatinine clearance, decreased white blood cell count, depression, dizziness, dysgeusia, dyspnea, hyperhidrosis, hypersensitivity reaction, hypocalcemia, increased amylase, increased gamma-glutamyl transferase, increased serum alanine aminotransferase, increased serum lipase, insomnia, neutropenia, palpitations, pancreatic necrosis, pleural effusion, prolonged partial thromboplastin time, skin rash

Drug Interactions^{1,2,3,4}:

Aminolevulinic Acid (Systemic): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Systemic). *Risk X: Avoid combination*

Aminolevulinic Acid (Topical): Photosensitizing Agents may enhance the photosensitizing effect of Aminolevulinic Acid (Topical). *Risk C: Monitor therapy*

BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). *Risk C: Monitor therapy*

Cholera Vaccine: Antibiotics may diminish the therapeutic effect of Cholera Vaccine. Management: Avoid cholera vaccine in patients receiving systemic antibiotics, and within 14 days following the use of oral or parenteral antibiotics. *Risk X: Avoid combination*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Eravacycline. Management: Increase the eravacycline dose to 1.5 mg/kg every 12 hours when combined

with strong CYP3A4 inducers. *Risk D: Consider therapy modification.* Note*: Theoretically, strong 3A4 inhibitors could interact, but are not included in interaction databases, and could increase levels of eravacycline, which could potentially increase side effects.

Lactobacillus and Estriol: Antibiotics may diminish the therapeutic effect of Lactobacillus and Estriol. *Risk C: Monitor therapy*

Mecamylamine: Tetracyclines may enhance the neuromuscular-blocking effect of Mecamylamine. *Risk X: Avoid combination*

Methoxyflurane: Tetracyclines may enhance the nephrotoxic effect of Methoxyflurane. *Risk X: Avoid combination*

Mipomersen: Tetracyclines may enhance the hepatotoxic effect of Mipomersen. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Tetracyclines may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracyclines may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Porfimer: Photosensitizing Agents may enhance the photosensitizing effect of Porfimer. *Risk C: Monitor therapy*

Retinoic Acid Derivatives: Tetracyclines may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern.

Adapalene; Bexarotene (Topical); Tretinoin (Topical). *Risk X: Avoid combination*

Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents. *Risk D: Consider therapy modification*

Verteporfin: Photosensitizing Agents may enhance the photosensitizing effect of Verteporfin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tetracyclines may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Dosing/Administration^{1,2,3,4}:

Adult Dosing

1 mg/kg IV every 12 hours for 4 to 14 days; the duration of therapy should be guided by the severity and location of infection and patient response

Pediatrics (≥4 years of age)

The safety and effectiveness of eravacycline in pediatric patients have not been established.

Elderly

No clinically significant differences in the pharmacokinetics of eravacycline were observed based on age (18 to 86 years).

Renal impairment

No adjustment necessary. The geometric least square mean C_{max} for eravacycline increased by 8.8% for patients with end-stage renal disease (ESRD) compared to healthy subjects, and the geometric least square mean AUC for eravacycline was decreased by 4% for patients with ESRD compared to healthy subjects.

Hepatic impairment

Mild to moderate, Child-Pugh A or B: No adjustments necessary.
Severe, Child-Pugh C: 1mg/kg every 12 hours on day 1, followed by 1 mg.kg every 24 hours on day 2 for a total of 4 to 14 days.

Gender Differences

No clinically significant differences in the pharmacokinetics of eravacycline were observed based on gender.

Ethnic Differences

No clinically significant differences in the pharmacokinetics of eravacycline were observed based on race.

Use in special circumstances^{1,2,3,4}:

Pregnancy:

Tetracyclines cross the placenta, and accumulate in teeth and long tubular bones. Exposure during 2nd and 3rd trimesters can cause reversible inhibition of bone growth. Permanent discoloration of teeth (yellow, gray, brown) can occur following in utero exposure and is more likely to occur following long-term or repeated exposure.

Lactation:

Infant risk cannot be ruled out as it is not known if eravacycline is present in breast milk. Other tetracyclines are present in breast milk, but the extent of absorption by infant is not known. Breastfeeding is not recommended by the manufacturer during therapy or for 4 days after last dose.

Conclusion:

Eravacycline is an effective antibiotic for patients presenting with cIAI. More studies need to be conducted to expand labeled indications for eravacycline for patients with other infectious presentations. Eravacycline, carries moderately the same safety profile as other tetracycline antibacterials. Like other tetracyclines, eravacycline decreases in efficacy requiring dose adjustments with concurrent strong CYP3A4 inducer use, and can enhance the effect of vitamin K antagonists. Eravacycline has an average wholesale price (AWP) of \$52.50 for 50mg, whereas a comparator product, such as meropenem has an AWP of \$13.20 - \$52.00 for 1g IV solution reconstituted. Overall, with its moderately minimal drug interaction and safety profile eravacycline appears to be an alternative tetracycline antibacterial that has a place in therapy for cIAI in patients who cannot tolerate or have failed other therapies.

Recommended References:

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5. Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, Sutcliffe JA, Horn P. 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 Mar 1; 152(3): 224-232
6. Solomkin J, Ramesh MK, Sutcliffe JA, et al. Phase 2, Randomized, Double-blind Study of The Efficacy and Safety of Two Dose Regimens of Eravacycline Versus Ertapenem for Adult Community-acquired Complicated Intra-Abdominal Infections. Antimicrob Agents Chemother. 2014; 58(4): 1847-1854.
7. Tetrphase Staff. Press Releases. Tetrphase Pharmaceuticals; February 13, 2018. Available at: <https://ir.tphase.com/news-releases/news-release-details/tetrphase-announces-top-line-results-ignite3-phase-3-clinical>. Accessed March 19, 2019.

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