

PRESCRIBING INFORMATION

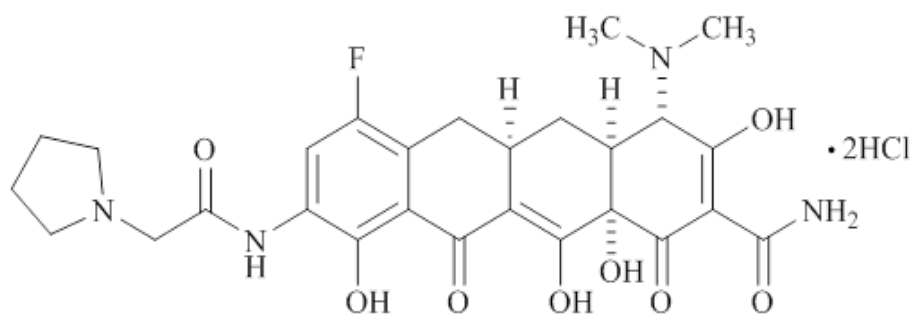
XERAVA POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 50 MG/VIAL

XERAVA Powder for concentrate for solution for infusion is a yellow to orange, sterile, preservative-free, lyophilized powder in single-dose vials containing 50 mg of eravacycline (equivalent to 63.5 mg eravacycline dihydrochloride) for reconstitution and further dilution.

1. DESCRIPTION

XERAVA contains eravacycline, a synthetic tetracycline-class antibacterial agent for intravenous administration. Chemically, eravacycline is a C7-, C9-substituted sancycline derivative. The chemical name of eravacycline dihydrochloride is [(4S,4aS,5aR,12aS)-4-(dimethylamino)-7-fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[2-(pyrrolidin-1-yl) acetamido]-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide] dihydrochloride.

The molecular formula for eravacycline dihydrochloride is $C_{27}H_{31}FN_4O_8 \cdot 2HCl$, and its molecular weight is 631.5. The following represents the chemical structure of eravacycline dihydrochloride:



XERAVA is a sterile, preservative-free, yellow to orange, lyophilized powder in a glass single- dose vial for intravenous infusion after reconstitution and dilution.

Each vial of XERAVA contains 50 mg of eravacycline (equivalent to 63.5 mg of eravacycline dihydrochloride) and the excipient, mannitol (150 mg). Sodium hydroxide and hydrochloric acid are used as needed for pH adjustment to 5.5 to 7.0.

2. INDICATIONS AND USAGE

2.1. Complicated Intra-abdominal Infections

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 [see Microbiology (10.4) and Clinical Studies (12.112)].

Limitations of Use

XERAVA is not indicated for the treatment of complicated urinary tract infections (cUTI) [see Clinical Studies (12.2)].

2.2. 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.

3. DOSAGE AND ADMINISTRATION

3.1. Recommended Adult Dosage

The recommended dose regimen of XERAVA is 1 mg/kg every 12 hours. Administer intravenous infusions of XERAVA over approximately 60 minutes every 12 hours.

The recommended duration of treatment with XERAVA for cIAI 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.

3.2. Dosage Modifications in Patients with Hepatic Impairment

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 mild to moderate hepatic impairment (Child Pugh A and Child Pugh B) [see Use in Specific Populations (8.6) and Clinical Pharmacology (10.3)].

3.3. Dosage Modifications in Patients with Concomitant Use of a Strong Cytochrome P450 Isoenzymes (CYP) 3A Inducer

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. No dosage adjustment is warranted in patients with concomitant use of a weak or moderate CYP3A inducer [see Drug Interactions (7.1) and Clinical Pharmacology (10.3)].

3.4. Preparation and Administration

XERAVA is for intravenous infusion only. Each vial is for a single dose only.

Preparation

XERAVA is supplied as a sterile yellow to orange dry powder in a single-dose vial that must be reconstituted and further diluted prior to intravenous infusion as outlined below. XERAVA does not contain preservatives. Aseptic technique must be used for reconstitution and dilution as follows:

1. Calculate the dose of XERAVA based on the patient weight; 1 mg/kg actual body weight. Prepare the required dose for intravenous infusion, by reconstituting the appropriate number of vials needed. Reconstitute each vial of XERAVA with 5 mL of Sterile Water for Injection, USP or with 5 mL of 0.9% Sodium Chloride Injection, USP. When the XERAVA vial content is reconstituted with 5 mL sterile Water for Injection, USP or with 5 mL of 0.9% Sodium Chloride Injection, USP, it will deliver 50 mg (10 mg/mL) of eravacycline (free base equivalents).
2. Swirl the vial gently until the powder has dissolved entirely. Avoid shaking or rapid movement as it may cause foaming. The reconstituted XERAVA solution should be a clear, pale yellow to orange solution. Do not use the solution if you notice any particles or the solution is cloudy. **Reconstituted solution is not for direct injection.** The stability of the solution after reconstitution in the vial has been demonstrated for 1 hour at room temperature (not to exceed 25°C). **If the reconstituted solution in the vial is not diluted in the infusion bag within 1 hour, the reconstituted vial content must be discarded.**
3. The reconstituted XERAVA solution is further diluted for intravenous infusion to a target

concentration of 0.3 mg/mL, in a 0.9% Sodium Chloride Injection, USP infusion bag before intravenous infusion. To dilute the reconstituted solution, withdraw the full or partial reconstituted vial content from each vial and add it into the infusion bag to generate an infusion solution with a target concentration of 0.3 mg/mL (within a range of 0.2 to 0.6 mg/mL). Do not shake the bag.

4. The diluted solutions must be infused within 24 hours if stored at room temperature (not to exceed 25°C) or within 7 days if stored refrigerated at 2°C to 8°C. Reconstituted XERAVA solutions and diluted XERAVA infusion solutions should not be frozen.
5. Visually inspect the diluted XERAVA solution for particulate matter and discoloration prior to administration (the XERAVA infusion solution for administration is clear and ranges from light yellow to orange). Discard unused portions of the reconstituted and diluted solution.

Administration of the Intravenous Infusion

The diluted XERAVA solution is administered as an intravenous infusion over approximately 60 minutes.

XERAVA may be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of XERAVA with 0.9% Sodium Chloride Injection, USP.

3.5. Drug Compatibilities

XERAVA is compatible with 0.9% Sodium Chloride Injection, USP.

The compatibility of XERAVA with other drugs and infusion solutions has not been established.

XERAVA should not be mixed with other drugs or added to solutions containing other drugs.

4. CONTRAINDICATIONS

XERAVA is contraindicated for use in patients with known hypersensitivity to eravacycline, tetracycline-class antibacterial drugs, or to any of the excipients [see Warnings and Precautions (5.1) and Adverse Reactions (6)].

5. WARNINGS AND PRECAUTIONS

5.1. Hypersensitivity Reactions

Life-threatening hypersensitivity (anaphylactic) reactions have been reported with XERAVA [see Adverse Reactions (6)]. XERAVA is structurally similar to other tetracycline-class antibacterial drugs and should be avoided in patients with known hypersensitivity to tetracycline-class antibacterial drugs. Discontinue XERAVA if an allergic reaction occurs.

5.2. Tooth Discoloration and Enamel Hypoplasia

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-grey-brown). This adverse reaction is more common during long-term use of the tetracycline class drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with tetracycline class drugs. Advise the patient of the potential risk to the fetus if XERAVA is used during the second or third trimester of pregnancy [see Use in Specific Populations (8.1, 8.4)].

5.3. Inhibition of Bone Growth

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. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Advise the patient of the potential risk to the fetus if XERAVA is used during the second or third trimester of pregnancy [see Use in Specific Populations (8.1, 8.4)].

5.4. *Clostridium difficile*-Associated Diarrhea

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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.5. Tetracycline Class Adverse Reactions

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.

5.6. Potential for Microbial Overgrowth

XERAVA use may result in overgrowth of non-susceptible organisms, including fungi. If such infections occur, discontinue XERAVA and institute appropriate therapy.

5.7. Development of Drug-Resistant Bacteria

Prescribing XERAVA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Indications and Usage (2.2)].

5.8. Pancreatitis

Pancreatitis has been reported with eravacycline and other tetracycline class antibiotics, and has been severe in some cases [see Adverse Reactions (6)]. If pancreatitis is suspected, eravacycline should be discontinued.

5.9. Concomitant use of strong CYP3A4 inducers

Medicines that induce CYP3A4 are expected to increase the rate and extent of metabolism of eravacycline. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline. Co-administration of a strong CYP3A4 inducer (such as phenobarbital, rifampicin, carbamazepine, phenytoin, St. John's Wort) is expected to reduce the effect of eravacycline [see Dosage and Administration (3.3), Drug Interactions (7.1) and Clinical Pharmacology (10.3)].

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in the Warnings and Precautions section:

- Hypersensitivity Reactions [Warning and Precautions (5.1)]
- Tooth Discoloration [Warning and Precautions (5.2)]
- Inhibition of Bone Growth [Warning and Precautions (5.3)]
- *Clostridium difficile*-Associated Diarrhea [Warning and Precautions (5.4)]
- Tetracycline Class Adverse Reactions [Warning and Precautions (5.5)]

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 may not reflect the rates observed in practice.

XERAVA was evaluated in 3 active-controlled clinical trials (Trial 1, Trial 2 and Trial 3) in adults with cIAI. These trials included two Phase 3 trials (Trial 1 and Trial 2) and one Phase 2 trial (Trial 3, NCT01265784). The Phase 3 trials included 520 patients treated with XERAVA and 517 patients treated with comparator antibacterial drugs (ertapenem or meropenem). The median age of patients treated with XERAVA was 56 years, ranging between 18 and 93 years old; 30% were age 65 years and older. Patients treated with XERAVA were predominantly male (57%) and Caucasian (98%). The XERAVA-treated population included 31% obese patients (BMI ≥ 30 kg/m²) and 8% with baseline moderate to severe renal impairment (calculated creatinine clearance 15 to less than 60 mL/min). Among the trials, 66 (13%) of patients had baseline moderate hepatic impairment (Child Pugh B); patients with severe hepatic impairment (Child Pugh C) were excluded from the trials.

Adverse Reactions Leading to Discontinuation

Treatment discontinuation due to an adverse reaction occurred in 2% (11/520) of patients receiving XERAVA and 2% (11/517) of patients receiving the comparator. The most commonly reported adverse reactions leading to discontinuation of XERAVA were related to gastrointestinal disorders.

Most Common Adverse Reactions

Adverse reactions occurring at 3% or greater in patients receiving XERAVA were infusion site reactions, nausea and vomiting.

Table 1 lists adverse reactions occurring in $\geq 1\%$ of patients receiving XERAVA and with incidences greater than the comparator in the Phase 3 cIAI clinical trials. A similar adverse reaction profile was observed in the Phase 2 cIAI clinical trial (Trial 3).

Table 1. Selected Adverse Reactions Reported in $\geq 1\%$ of Patients Receiving XERAVA in the Phase 3 cIAI Trials (Trial 1 and Trial 2)

Adverse Reactions	XERAVA ^a N=520 n (%)	Comparators ^b N=517 n (%)
Infusion site reactions ^c	40 (7.7)	10 (1.9)

Nausea	34 (6.5)	3 (0.6)
Vomiting	19 (3.7)	13 (2.5)
Diarrhea	12 (2.3)	8 (1.5)
Hypotension	7 (1.3)	2 (0.4)
Wound dehiscence	7 (1.3)	1 (0.2)

Abbreviations: IV=intravenous

^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.

Other Adverse Reactions of XERAVA

The following selected adverse reactions were reported in XERAVA-treated patients at a rate of less than 1% in the Phase 3 trials:

- Cardiac disorders: palpitations
- Gastrointestinal System: acute pancreatitis, pancreatic necrosis
- General Disorders and Administrative Site Conditions: chest pain
- Immune system disorders: hypersensitivity
- Laboratory Investigations: increased amylase, increased lipase, increased alanine aminotransferase, prolonged activated partial thromboplastin time, decreased renal clearance of creatinine, increased gamma-glutamyltransferase, decreased white blood cell count, neutropenia
- Metabolism and nutrition disorders: hypocalcemia
- Nervous System: dizziness, dysgeusia
- Psychiatric disorders: anxiety, insomnia, depression
- Respiratory, Thoracic, and Mediastinal System: pleural effusion, dyspnea
- Skin and subcutaneous tissue disorders: rash, hyperhidrosis

7. DRUG INTERACTIONS

7.1. Effect of Strong CYP3A Inducers on XERAVA

Concomitant use of strong CYP3A inducers decreases the exposure of eravacycline, which may reduce the efficacy of XERAVA [see Clinical Pharmacology (10.3)]. Increase XERAVA dose in patients with concomitant use of a strong CYP3A inducer [see Dosage and Administration (3.3)].

7.2. Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

XERAVA, like other tetracycline-class antibacterial drugs, may cause discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimester of pregnancy [see Warnings and Precautions (5), Data, Use in Specific Populations (8.4)]. The limited available data with XERAVA use in pregnant women are insufficient to inform drug-associated risk of major birth defects and miscarriages. Animal studies indicate that eravacycline crosses the placenta and

is found in fetal plasma; doses greater than approximately 3- and 2.8- times the clinical exposure, based on AUC in rats and rabbits, respectively, administered during the period of organogenesis, were associated with decreased ossification, decreased fetal body weight, and/or increased post-implantation loss [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

- *Animal Data*

Embryo-fetal development studies in rats and rabbits reported no treatment-related effects at approximately 3 and 2.8 times the clinical exposure (based on AUC). Dosing was during the period of organogenesis, i.e. gestation days 7-17 in rats and gestation days 7-19 in rabbits.

Higher doses, approximately 8.6 and 6.3 times the clinical exposure (based on AUC) in rats and rabbits, respectively, were associated with fetal effects including increased post-implantation loss, reduced fetal body weights, and delays in skeletal ossification in both species, and abortion in the rabbit.

A peri-natal and post-natal rat toxicity study demonstrated that eravacycline crosses the placenta and is found in fetal plasma following intravenous administration to the dams. This study did not demonstrate anatomical malformations, but there were early decreases in pup weight that were later comparable to controls and a non-significant trend toward increased stillbirths or dead pups during lactation. F1 males from dams treated with 10 mg/kg/day eravacycline that continued to fertility testing had decreased testis and epididymis weights at approximately Post- Natal Day 111 that may have been at least partially related to lower body weights in this group.

Tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy.

8.2. Lactation

Risk Summary

It is not known whether XERAVA is excreted in human breast milk. Eravacycline (and its metabolites) is excreted in the milk of lactating rats (*see Data*). Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including eravacycline, by the breastfed infant is not known. There are no data on the effects of XERAVA on the breastfed infant, or the effects on milk production. Because there are other antibacterial drug options available to treat cIAI in lactating women and because of the potential for serious adverse reactions, including tooth discoloration and inhibition of bone growth, advise patients that breastfeeding is not recommended during treatment with XERAVA and for 4 days (based on half-life) after the last dose.

Data

- *Animal Data*

Eravacycline (and its metabolites) was excreted in the milk of lactating rats on post-natal day 15 following intravenous administration of 3, 5, and 10 mg/kg/day eravacycline.

8.3. Females and Males of Reproductive Potential

Infertility

Based on animal studies, XERAVA can lead to impaired spermiation and sperm maturation, resulting in abnormal sperm morphology and poor motility. The effect is reversible in rats. The long-term effects of XERAVA on male fertility have not been studied [see Nonclinical Toxicology (11.1)].

8.4. Pediatric Use

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

Due to the adverse effects of the tetracycline-class of drugs, including XERAVALA on tooth development and bone growth, use of XERAVALA in pediatric patients less than 8 years of age is not recommended [see Warnings and Precautions (5.2, 5.3)].

8.5. Geriatric Use

Of the total number of patients with cIAI who received XERAVALA in Phase 3 clinical trials (n = 520), 158 subjects were ≥65 years of age, while 59 subjects were ≥75 years of age. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

No clinically relevant differences in the pharmacokinetics of eravacycline were observed with respect to age in a population pharmacokinetic analysis of eravacycline [see Clinical Pharmacology (10.3)].

8.6. Hepatic Impairment

No dosage adjustment is warranted for XERAVALA in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). Adjust XERAVALA dosage in patients with severe hepatic impairment (Child Pugh C) [see Dosage and Administration (3.2) and Clinical Pharmacology (10.3)].

8.7. Renal Impairment

No dosage adjustment is necessary for XERAVALA in patients with renal impairment [see Clinical Pharmacology (10.3)].

9. OVERDOSAGE

No reports of overdose were reported in clinical trials. In the case of suspected overdose, XERAVALA should be discontinued and the patient monitored for adverse reactions. Hemodialysis is not expected to remove significant quantities of XERAVALA [see Clinical Pharmacology (10.3)].

10. CLINICAL PHARMACOLOGY

10.1. Mechanism of Action

Eravacycline is an antibacterial drug [see Microbiology (10.4)].

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines, ATC code: J01AA13.

10.2. Pharmacodynamics

The AUC divided by the MIC of eravacycline has been shown to be the best predictor of activity. Based on the flat exposure-response relationship observed in clinical studies, eravacycline exposure achieved with the recommended dosage regimen appears to be on the plateau of the exposure-response curve.

Cardiac Electrophysiology

The effect of XERAVALA on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, single-dose, crossover thorough QTc study in 60 healthy adult subjects. At the 1.5 mg/kg single dose (1.5 times the maximum approved recommended dose), XERAVALA did not prolong the QTc interval to any clinically relevant extent.

10.3. Pharmacokinetics

Following single-dose intravenous administration, eravacycline AUC and $C_{\max}$ increase approximately dose-proportionally over doses from 1 mg/kg to 3 mg/kg (3 times the approved dose).

The mean exposure of eravacycline after single and multiple intravenous infusions (approximately 60 minutes) of 1 mg/kg administered to healthy adults every 12 hours is presented in Table 2.

There is approximately 45% accumulation following intravenous dosing of 1 mg/kg every 12 hours.

Table 2 Mean (%CV) Plasma Exposure of Eravacycline After Single and Multiple Intravenous Dose in Healthy Adults

Exposure [Arithmetic Mean (%CV)]		
	$C_{\max}$ (ng/mL)	AUC ₀₋₁₂ (ng·h/mL)
Day 1	2125 (15)	4305 (14) ^a
Day 10	1825 (16)	6309 (15) ^b

Abbreviations: $C_{\max}$ = maximum observed plasma concentration, CV = coefficient of variation; AUC₀₋₁₂ = area under the plasma concentration-time curve from time 0 to 12 hours.

^aAUC of day 1 equals AUC₀₋₁₂ after the first dose of eravacycline.

^bAUC of day 10 equals steady state AUC₀₋₁₂.

Distribution

Protein binding of eravacycline to human plasma proteins increases with increasing plasma concentrations, with 79% to 90% (bound) at plasma concentrations ranging from 100 to 10,000 ng/mL. The volume of distribution at steady-state is approximately 321 L.

Elimination

The mean elimination half-life is 20 hours.

Metabolism

Eravacycline is metabolized primarily by CYP3A4- and FMO-mediated oxidation.

Excretion

Following a single intravenous dose of radiolabeled eravacycline 60 mg, approximately 34% of the dose is excreted in urine and 47% in feces as unchanged eravacycline (20% in urine and 17% in feces) and metabolites.

Specific Populations

No clinically significant differences in the pharmacokinetics of eravacycline were observed based on age (18-86 years), sex, and race.

- *Patients with Renal Impairment*

The geometric least square mean $C_{\max}$ for eravacycline was increased by 8.8% for subjects with end stage renal disease (ESRD) versus healthy subjects with 90% CI -19.4, 45.2. The geometric least square mean AUC_{0-inf} for eravacycline was decreased by 4.0% for subjects with ESRD versus healthy subjects with 90% CI -14.0, 12.3 [see Use in Specific Populations (8.7)].

- *Patients with Hepatic Impairment*

Eravacycline $C_{\max}$ was 13.9%, 16.3%, and 19.7% higher in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment versus healthy subjects, respectively. Eravacycline AUC_{0-inf} was 22.9%, 37.9%, and 110.3% higher in subjects with mild, moderate, and severe hepatic impairment versus healthy subjects, respectively [see Dosage and Administration (3.2) and Use in Specific Populations (8.6)].

Drug Interaction Studies

- *Clinical Studies*

Concomitant use of rifampin (strong CYP3A4/3A5 inducer) decreased eravacycline AUC by 35% and increased eravacycline clearance by 54% [see Dosage and Administration (3.3) and Drug Interactions (7.1)].

Concomitant use of itraconazole (strong CYP3A inhibitor) increased eravacycline C_{max} by 5% and AUC by 32%, and decreased eravacycline clearance by 32%.

- *In Vitro Studies*

Eravacycline is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Eravacycline is not an inducer of CYP1A2, 2B6, or 3A4.

Eravacycline is not a substrate for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter peptide (OATP)1B1, OATP1B3, organic ion transporter (OAT)1, OAT3, OCT1, OCT2, multidrug and toxin extrusion (protein) (MATE)1, or MATE2-K transporters.

Eravacycline is not an inhibitor of BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K transporters.

10.4. Microbiology

Mechanism of Action

Eravacycline is a fluorocycline antibacterial within the tetracycline class of antibacterial drugs. Eravacycline disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit thus preventing the incorporation of amino acid residues into elongating peptide chains.

In general, eravacycline is bacteriostatic against gram-positive bacteria (e.g., *Staphylococcus aureus* and *Enterococcus faecalis*); however, in vitro bactericidal activity has been demonstrated against certain strains of *Escherichia coli* and *Klebsiella pneumoniae*.

Resistance

Eravacycline resistance in some bacteria is associated with upregulated, non-specific intrinsic multidrug-resistant (MDR) efflux, and target-site modifications such as to the 16s rRNA or certain 30S ribosomal proteins (e.g., S10).

The C7 and C9 substitutions in eravacycline are not present in any naturally occurring or semisynthetic tetracyclines and the substitution pattern imparts microbiological activities including in vitro activity against gram-positive and gram-negative strains expressing certain tetracycline-specific resistance mechanism(s) [i.e., efflux mediated by *tet(A)*, *tet(B)*, and *tet(K)*; ribosomal protection as encoded by *tet(M)* and *tet(Q)*].

Activity of eravacycline was demonstrated in vitro against Enterobacteriaceae in the presence of certain beta-lactamases, including extended spectrum β -lactamases, and AmpC. However, some beta-lactamase-producing isolates may confer resistance to eravacycline via other resistance mechanisms.

The overall frequency of spontaneous mutants in the gram-positive organisms tested was in the range of 10^{-9} to 10^{-10} at 4 times the eravacycline Minimum Inhibitory Concentration (MIC).

Multistep selection of gram-negative strains resulted in a 16- to 32-times increase in eravacycline MIC for one isolate of *Escherichia coli* and *Klebsiella pneumoniae*, respectively. The frequency of spontaneous mutations in *K. pneumoniae* was 10^{-7} to 10^{-8} at 4 times the eravacycline MIC.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between XERAVA and other commonly used antibacterial drugs for the indicated pathogens.

Antimicrobial Activity

XERAVA has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [see Indications and Usage (2)]:

Aerobic bacteria

Gram-positive bacteria

- o *Enterococcus faecalis*
- o *Enterococcus faecium*
- o *Staphylococcus aureus*
- o *Streptococcus anginosus* group

Gram-negative bacteria

- o *Citrobacter freundii*
- o *Enterobacter cloacae*
- o *Escherichia coli*
- o *Klebsiella oxytoca*
- o *Klebsiella pneumoniae*

Anaerobic bacteria

Gram-positive bacteria

- o *Clostridium perfringens*

Gram-negative bacteria

- o *Bacteroides caccae*
- o *Bacteroides fragilis*
- o *Bacteroides ovatus*
- o *Bacteroides thetaiotaomicron*
- o *Bacteroides uniformis*
- o *Bacteroides vulgatus*
- o *Parabacteroides distasonis*

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 eravacycline against isolates of similar genus or organism group. However, the efficacy of eravacycline in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria

- o *Streptococcus salivarius* group

Gram-negative bacteria

- o *Citrobacter koseri*
- o *Enterobacter aerogenes*

11. NONCLINICAL TOXICOLOGY

11.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with eravacycline have not been conducted. However, there has been evidence of

oncogenic activity in rats in studies with the related antibacterial drugs, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors).

Eravacycline was not genotoxic in a standard battery of assays, including an in vitro mammalian cell mutation assay, an in vitro clastogenicity assay, and an in vivo rat bone marrow micronucleus assay.

There are no human data on the effect of eravacycline on fertility. Eravacycline did not affect mating or fertility in male rats following intravenous administration at a dose approximating a clinical dose of 0.65 mg/kg/day (approximately 1.5 times the clinical exposure, based on AUC determined in a separate study), however, eravacycline administration at higher doses was associated with adverse reactions on male fertility and spermatogenesis that were at least partially reversible after a 70-day recovery period (1 spermatogenic cycle). Decreased sperm counts, abnormal sperm morphology, and reduced sperm motility were observed with testicular effects (impaired spermiation and sperm maturation). There were no adverse reactions on mating or fertility in female rats administered intravenous eravacycline at a dose approximating a clinical dose of 3.2 mg/kg/day (approximately 18 times the clinical exposure based on AUC determined in a separate study in unmated females).

Decreased sperm counts and eravacycline-related lesions noted in the testes and epididymides were seen in general toxicology studies in rats and were reversible. These findings were anticipated effects for a tetracycline-class compound.

11.2. Animal Toxicology and/or Pharmacology

In repeated dose toxicity studies in rats, dogs and monkeys, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets (dog and monkey), in association with bone marrow hypocellularity, and adverse gastrointestinal effects (dog and monkey) were observed with eravacycline. These findings were reversible or partially reversible during recovery periods of 3 to 7 weeks.

Bone discoloration, which was not fully reversible over recovery periods of up to 7 weeks, was observed in rats and monkeys after 13 weeks of dosing and in the juvenile rat study after dosing over Post-Natal Days 21-70.

Intravenous administration of eravacycline has been associated with a histamine response in rat and dog studies.

12. CLINICAL STUDIES

12.1. Complicated Intra-abdominal Infections in Adults

A total of 1,041 adults hospitalized with cIAI were enrolled in two Phase 3, randomized, double-blind, active-controlled, multinational, multicenter trials (Trials 1, NCT01844856, and Trial 2, NCT02784704). These studies compared XERAVA (1 mg/kg intravenous every 12 hours) with either ertapenem (1 g every 24 hours) or meropenem (1 g every 8 hours) as the active comparator for 4 to 14 days of therapy. Complicated intra-abdominal infections included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis.

The microbiologic intent-to-treat (micro-ITT) population, which included all patients who had at least one baseline intra-abdominal pathogen, consisted of 846 patients in the two trials.

Populations in Trial 1 and Trial 2 were similar. The median age was 56 years and 56% were male. The majority of patients (95%) were from Europe; 5% were from the United States. The most common primary cIAI diagnosis was intra-abdominal abscess(es), occurring in 60% of patients. Bacteremia at baseline was present in 8% of patients.

Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection at the Test of Cure (TOC) visit which occurred 25 to 31 days after randomization. Selected clinical responses were reviewed by a Surgical Adjudication Committee. Table 3 presents the clinical cure rates in the micro-ITT population. Clinical cure rates at the TOC visit for selected pathogens are presented in Table 4.

Table 3 Clinical Cure Rates at TOC in the Phase 3 cIAI Trials, Micro-ITT Population

	Trial 1		Trial 2	
	XERAVA ^a N=220 n (%)	Ertapenem ^b N=226 n (%)	XERAVA ^a N=195 n (%)	Meropenem ^c N=205 n (%)
Clinical cure	191 (86.8)	198 (87.6)	177 (90.8)	187 (91.2)
Difference (95% CI) ^d	-0.80 (-7.1, 5.5)		-0.5 (-6.3, 5.3)	

Abbreviations: CI = confidence interval; IV = intravenous; micro-ITT = all randomized subjects who had baseline bacterial pathogens that caused cIAI and against at least one of which the investigational drug has in vitro antibacterial activity; N = number of subjects in the micro-ITT population; n = number within a specific category with a clinical cure based on the Surgical Adjudication Committee assessment (if available); TOC=Test of Cure.

^a XERAVA dose equals 1 mg/kg every 12 hours IV.

^b Ertapenem dose equals 1 g every 24 hours IV

^c Meropenem dose equals 1 g every 8 hours IV.

^d Treatment Difference = Difference in clinical cure rates (eravacycline minus ertapenem or meropenem).

Confidence intervals are calculated using the unadjusted Miettinen-Nurminen method

Table 4 Clinical Cure Rates at TOC by Selected Baseline Pathogens in Pooled Phase 3 cIAI Trials, Micro-ITT Population

Pathogen	XERAVA ^a N=415 n/N1 (%)	Comparators ^b N=431 n/N1 (%)
Enterobacteriaceae	271/314 (86.3)	289/325 (88.9)
<i>Citrobacter freundii</i>	19/22 (86.4)	8/10 (80.0)
<i>Enterobacter cloacae</i> complex	17/21 (81.0)	23/24 (95.8)
<i>Escherichia coli</i>	220/253 (87.0)	237/266 (89.1)
<i>Klebsiella oxytoca</i>	14/15 (93.3)	16/19 (84.2)
<i>Klebsiella pneumoniae</i>	37/39 (94.9)	42/50 (84.0)
<i>Enterococcus faecalis</i>	45/54 (83.3)	47/54 (87.0)
<i>Enterococcus faecium</i>	38/45 (84.4)	48/53 (90.6)
<i>Staphylococcus aureus</i>	24/24 (100.0)	12/14 (85.7)
<i>Streptococcus anginosus</i> group ^c	79/92 (85.9)	50/59 (84.7)
Anaerobes ^d	186/215 (86.5)	194/214 (90.7)

Abbreviations: IV = intravenous; N = Number of subjects in the micro-ITT Population; N1 = Number of subjects with a specific pathogen; n = Number of subjects with a clinical cure at the TOC visit. Percentages are calculated as $100 \times (n/N1)$; TOC = Test of Cure

^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 Includes *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*

^d Includes *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Parabacteroides distasonis*.

12.2. Complicated Urinary Tract Infections (cUTI) in Adults

Two randomized, double-blind, active-controlled, clinical trials (Trial 4, NCT01978938, and Trial 5, NCT03032510) evaluated the efficacy and safety of once-daily intravenous eravacycline for the treatment of patients with complicated urinary tract infections (cUTI). Trial 4 included an optional switch from IV to oral therapy with eravacycline. The trials did not demonstrate the efficacy of XERAVAL for the combined endpoints of clinical cure and microbiological success in the microbiological intent-to-treat (micro-ITT) population at the test-of-cure visit [see Indications and Usage (2)].

13. SHELF LIFE

3 years.

The stability of the solution after reconstitution in the vial has been demonstrated for 1 hour at room temperature (not to exceed 25°C). If the reconstituted solution in the vial is not diluted in the infusion bag within 1 hour, the reconstituted vial content must be discarded [See Preparation and Administration (3.4)].

The diluted solutions must be infused within 24 hours if stored at room temperature (not to exceed 25°C) or within 7 days if stored refrigerated at 2°C to 8°C. Reconstituted XERAVAL solutions and diluted XERAVAL infusion solutions should not be frozen [See Preparation and Administration (3.4)].

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

14. SPECIAL PRECAUTIONS FOR STORAGE

Prior to reconstitution, XERAVAL should be stored in a refrigerator (2–8°C). Keep the vial in the carton in order to protect from light.

For storage conditions after reconstitution and dilution of XERAVAL, see above section on Shelf life.

15. HOW SUPPLIED

XERAVAL Powder for concentrate for solution for infusion is supplied as a yellow to orange, sterile, preservative-free, lyophilized powder in a single-dose vial (10mL Type I glass vial with chlorobutyl rubber stopper and aluminium cap).

Each vial contains 50 mg of eravacycline (equivalent to 63.5 mg of eravacycline dihydrochloride).

15.1. List of excipients

- Mannitol (E421)
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)

15.2. Packsizes

XERAVA is supplied in two packsizes:

- Single-vial carton containing one 50 mg single-dose vial
- Twelve-vial carton containing twelve 50 mg single-dose vial cartons

Not all packsizes may be available locally.

16. PRODUCT REGISTRANT

Everest Medicines (Singapore) Pte. Ltd.
30 Cecil Street, #19-08
Prudential Tower
Singapore 049712

17. DATE OF REVISION OF THE TEXT

30 April 2020