Class Review: Tetracycline Antibiotics **April 2020**

Executive Summary: Criteria for Formulary Consideration of Tetracycline Drug Class

Introduction

This review is to update the Nebraska Medicine formulary status of current agents in the tetracycline class:

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
Formulary status	Oral/IV: Formulary	IV: Not yet considered	Oral: Formulary IV: Non-formulary	Oral/IV: Not yet considered	Oral: Not yet considered	Oral: Non-formulary	IV: Formulary (restricted)

There have been a number of newly marketed therapies in this class since the prior review, so this document will focus primarily on review of those agents and compare/contrast them with the characteristics of the established tetracyclines.

Efficacy

Clinical trials are summarized below. Eravacycline showed noninferiority to ertapenem for treatment of complicated intra-abdominal infections and was noninferior to meropenem in the treatment of adults with complicated intra-abdominal infections, including infections caused by resistant pathogens. Omadacycline was noninferior compared to moxifloxacin for the treatment of community-acquired bacterial pneumonia in adults and was well tolerated and effective for treating patients with serious skin and soft tissue infections compared to linezolid. Sarecycline was effective, safe, and well tolerated for moderate to severe acne.

Safety

All tetracyclines should be avoided during pregnancy due to reduced bone growth. Tetracyclines should also be avoided in patients 8 years old and younger due to tissue hyperpigmentation, tooth enamel hypoplasia, and permanent tooth discoloration. Based on pooled analysis of Phase III and IV clinical trials, the United States Food and Drug Administration issued a Boxed Warning in 2010 for increased risk of mortality associated with tigecycline use. The studies showed increased mortality in patients with hospital-acquired and ventilator-associated pneumonia, complicated intra-abdominal infections, and diabetic foot infections. In the pooled analysis, mortality was 4% (150/3788) in patients receiving tigecycline versus 3% (110/3646) in patients receiving comparator drugs. Additional studies were analyzed in 2013, and increased mortality was still seen in tigecycline vs comparator drugs (2.5% [66/2640] vs 1.8% [48/2628]). The exact cause of the excess deaths is uncertain, but they are generally attributed to worsening infections or complications associated with infections. Therefore, it is not typically recommended as monotherapy for severe infections.

Uniqueness

Tetracyclines are broad-spectrum antibiotics that have a bacteriostatic effect on a wide variety of susceptible bacterial organisms. While there are many similarities among drugs within the class, some, including the newer agents (omadacycline, eravacycline, and sarecycline), have unique features as outlined below.

- Minocycline has a reintroduced IV formulation and established activity against multidrug resistant *Acinetobacter spp.* isolates, particularly with an indication of pneumonia.
- Tigecycline is a tetracycline antibiotic that belongs to the glycylcycline class. It has a broader spectrum of activity than older tetracyclines in the class such as doxycycline or minocycline and is not affected by ribosomal protection proteins or many efflux pumps, offering less potential for resistance.
- Omadacycline has been shown to be non-inferior to moxifloxacin when treating community-acquired bacterial pneumonia and just as effective as linezolid when treating skin infections. Its unique chemical structure allows it to overcome resistance mechanisms used against doxycycline and minocycline, including drug efflux and ribosomal protection. It has activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB) and extended-spectrum beta-lactamase-producing organisms (ESBL's), as does eravacycline below. Its structure also increases antibacterial potency and decreases adverse effects when compared to tigecycline. Omadacycline offers an oral dosage form that can be used to treat numerous community-acquired infections, including those caused by multidrug resistant organisms, giving it a useful niche. Recent *in vitro* data also suggest that it has activity against rapidly-growing *Mycobacterium spp.*, but more data is needed before using this as routine treatment of infections caused by this organism. It would be clinically useful to have an additional oral agent for the treatment of *Mycobacterial* infections.

- Eravacycline has been shown to be similarly efficacious to carbapenems for complicated intra-abdominal infections; however, it was inferior to levofloxacin in the treatment of complicated urinary tract infections. It is structurally similar to tigecycline with two modifications that impart increased antibacterial potency and decreased adverse effects, chiefly nausea and vomiting. There is currently no Boxed Warning or evidence for increased mortality associated with eravacycline. It has activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB) and extended-spectrum beta-lactamase-producing organisms (ESBL's), as for omadacycline above. Also as with omadacycline, some *in vitro* data show activity against rapidly-growing *Mycobacterium spp.*, but more studies are needed before routinely using this agent in these scenarios.
- Sarecycline is labeled for the treatment of moderate to severe non-nodular acne vulgaris. Similar to other tetracyclines, it has activity against *Cutibacterium acnes*, including macrolide-resistant strains, and *Staphylococcus spp.*; its distinction, however, is its significantly narrower spectrum compared with other tetracyclines. It displays a 16- to 32-fold decrease in activity against aerobic gram-negative rods of the human GI microbiome and a 4- to 8-fold decrease in GI anaerobic activity when compared to other tetracyclines. It is also less affected by usual tetracycline resistance mechanisms. This low propensity for resistance and narrow spectrum of activity allows for a more targeted approach to treat acne vulgaris with minimal impact on normal intestinal flora.

Cost

	Doxycycline	**Eravacycline**	**Minocycline**	**Omadacycline**	**Sarecycline**	**Tetracycline**	**Tigecycline**
Cost per day (based on maintenance dosing AWP)	IV: $50.40 PO: $2.16	IV: $235.20	IV: $389.12 PO: $3.76	IV: $452.39 PO: $544.80	PO: $37.56	PO: $31.52	IV: $80.00

Recommendations

1. No change recommended to the formulary status of the established tetracycline agents. Tigecycline is expected to retain an inpatient role as a cost-effective IV therapy for patients requiring the spectrum of the newer tetracycline agents and that can tolerate its somewhat less favorable adverse effect profile.
2. Recommend omadacycline be added to formulary based on its antimicrobial spectrum, lack of significant resistance, availability as an oral dosage form, and potential for use in difficult to treat multidrug-resistant and mycobacterial infections. We recommend that it be added with a restriction to infectious diseases specialists to prevent unnecessary use when equally effective and less expensive alternatives (e.g. doxycycline) exist.
3. Recommend eravacycline not be added to formulary at this time. Its main beneficial roles could be for use against carbapenem-resistant *Acinetobacter baumannii* or as a carbapenem-sparing option for ESBL-producing organisms; however, Nebraska currently has a low incidence of CRAB, and based on cost-benefit analysis, carbapenems may be a better option for ESBL's than eravacycline. The rarely needed benefits of this IV-only formulation could likely be met by either tigecycline or omadacycline.
4. Recommend sarecycline not be added to formulary based on the lack of need for an inpatient drug with its activity and indication.

The authors of this document have no financial relationship with pharmaceutical companies, biomedical device manufacturers, or distributors or others whose products or services may be considered related to the subject matter within.

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Introduction[1-7]

Tetracyclines are broad-spectrum antibiotics that have a bacteriostatic effect on a wide variety of susceptible bacterial organisms.[1] They work by entering the bacterial cell wall via passive diffusion and active transport. After they enter the bacterial cell, they bind to the 30S ribosomal subunit which results in the inhibition of protein synthesis. Tetracyclines are used to treat susceptible infections caused by a variety of gram-positive and gram-negative bacteria, as well as atypical pathogens, such as *Rickettsia* spp, *Chlamydia* spp, and *Mycoplasma pneumoniae*.[1] Resistance to tetracyclines occurs when accumulation of the drug inside the cell is stopped by increasing efflux or decreasing influx.[2] Some bacteria have resistance genes that produce cytoplasmic proteins which allow ribosomes to synthesize protein even when tetracyclines are present.

Tigecycline is a tetracycline antibiotic that belongs to the glycylcycline class.[3] It has a broader spectrum of activity than other tetracyclines in the class. Tigecycline is not affected by ribosomal protection proteins or many efflux pumps which offers less potential for resistance. It may be active against some organisms that are resistant to tetracycline. Certain bacteria, such as *Proteus*, may become resistant to tigecycline via overexpression of chromosomally encoded multidrug efflux pumps.[3] Newer agents of the tetracycline antibiotic class include eravacycline and omadacycline. These agents were approved by FDA in 2018.[1] As with tigecycline, the newer tetracycline derivatives are broadly active against a number of typical and MDR pathogens (see table below), such as MRSA, VRE, extended-spectrum beta-lactamase-producing organisms and carbapenem-resistant *Acinetobacter baumannii*. Eravacycline is a fluorocycline antibiotic that belongs to tetracycline class.[4] It is approved for complicated intra-abdominal infections and has similar cure rates to carbapenems.[4] Omadacycline is approved for the treatment of community-acquired bacterial pneumonia and was shown to be non-inferior to moxifloxacin in a clinical trial studying community-acquired bacterial pneumonia.[6] It is also approved for the treatment of skin and skin structure infections.[7]

Sarecycline is labeled for the treatment of moderate to severe non-nodular acne vulgaris in patients that are at least 9 years old.[1]

Formulary Status

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
Formulary status	Formulary	Not yet considered	Oral: Formulary IV: Non-formulary	Not yet considered	Not yet considered	Non-formulary	Formulary (restricted)

Antimicrobial Spectra of the Tetracyclines†

	Staph (incl. MRSA)	Strep	Enterococcus		H. influenza M. catarrhalis	Enterobacteriaceae				Pseudomonas	Acinetobacter sp. (incl. CRAB)	S. maltophilia	Atypicals	Non-tuberculosis Mycobacteria
			VSE	VRE		ESBL	AmpC	CRE	NDM					
Doxycycline	✓	✓	✓	+/-	✓	+/-	+/-	+/-	+/-	X	+/-	✓	✓	+/-
Eravacycline	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓
Minocycline	✓	✓	✓	+/-	✓	+/-	+/-	+/-	+/-	X	✓	✓	✓	+/-
Omadacycline	✓	✓	✓	✓	✓	✓	✓	++/-	++/-	X	✓	✓	✓	✓
Sarecycline	✓	✓	X	X	X	X	X	X	X	X	X	X	X	X
Tetracycline	✓	✓	+/-	+/-	✓	+/-	+/-	+/-	+/-	X	+/-	X	✓	X
Tigecycline	✓	✓	✓	✓	✓	✓	✓	++/-	✓	X	✓	✓	✓	✓

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VSE, vancomycin-susceptible *Enterococcus*; VRE, vancomycin-resistant *Enterococcus*; ESBL, extended spectrum beta-lactamase; CRE, carbapenem-resistant Enterobacteriaceae; NDM, New Delhi metallo-beta-lactamase; CRAB, carbapenem-resistant *Acinetobacter baumanii*
†Activity reflects general trends; always defer to antimicrobial susceptibility testing to support clinical decisions

Pharmacokinetics[8-15]

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
Absorption	Almost completely absorbed from GI tract. Reduced 20% with high-fat meal or milk.	N/A	Oral: Well absorbed	Do not eat for 4hrs before or 2hrs after dosing. Reduced exposure by ~50%.	Not reported	Oral: 77-88% Reduced 50% if administered with food	N/A
Metabolism	Not hepatic. Partially inactivated by chelate formation in GI tract	CYP3A4 primarily and FMO- mediated oxidation	Hepatic to inactive metabolites	None	Minimal (<15%)	None	Hepatic via glucuronidation, N-acetylation, and epimerization
Elimination	Feces 30% Urine 23-40%	Feces 47% Urine 34%	Feces 20-34% Urine 5-12% excreted unchanged	IV: urine (27% unchanged drug) Oral: feces (77.5-84%), urine (10.8-17.4%)	Feces 42.6% Urine 44.1%,	Feces 20-60% Urine 30%	Feces 59% unchanged drug Urine 33%,
Tmax (hrs)	Immediate release: 1.5-4 Delayed release: 2.8-3	N/A	Capsule, pellet-filled: 1-4 Tablet: 1-3 Tablet, Extended release: 3.5-4	IV: 0.5 Oral: 2.5	1.5-2 0.53-hour delay when administered with high-fat, high-calorie meal that included milk	Oral: 2-4	N/A
Half-life (hrs)	18-22 End-stage renal disease: 18-25	20	IV: 15-23, 11-16 (hepatic impairment), 18-69 (renal impairment) Oral: 11-17	IV: 16 Oral: 13.45-16.83	21-22	6-11	Single dose: 27 Multiple doses: 42 Increased 23% in moderate hepatic impairment Increased 43% in severe hepatic impairment

Selected FDA Approved Indications[8-23]

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
Year of FDA approval	1967	2018	1971	2018	2018	1953	2005
Acne	X		X		X	X	
Acute intestinal amebiasis	X					X	
Endocarditis	X						
Intra-abdominal Infections		X					X
Listeriosis	X		X			X	
Mycoplasma pneumonia	X						

Ophthalmic Infections	X		X			X	
Pneumonia (Community Acquired)	X			X			X
Respiratory Tract Infections	X		X			X	
Rickettsial Infections	X		X			X	
Sexually Transmitted Infections	X		X			X	
Skin and Skin Structure Infections	X		X	X		X	X
Urinary Tract Infections			X			X	

Clinical Trials and Guidelines [4, 6, 7, 24, 25, 26, 27, 28]

Study Design	Methods	Results	Conclusions
IGNITE 1 Phase III, randomized, double-blind, multicenter trial to study the efficacy and safety of eravacycline compared with ertapenem in patients with complicated intra-abdominal infections (cIAI) N=541 (270 in eravacycline group, 271 in ertapenem group) Noninferiority margin of 10%	**Inclusion Criteria**: hospitalized for cIAI infection requiring intervention, 18 years or older, evidence of systemic inflammatory response, pain caused by cIAI, able to provide informed consent, and diagnosis of cIAI with sonogram or radiographic imaging. **Exclusion Criteria**: rapidly progressing disease or immediately life-threatening illness including hepatic failure, respiratory failure, and/or septic shock; requirement of vasopressors to maintain systolic blood pressure at least 90 mmHg or diastolic blood pressure at least 70 mmHg; CrCl less than 50 mL/min; signs of significant hepatic disease (AST/ALT greater than 3 times the upper limits of normal or greater than 5 times the upper limits of normal for patients with hepatic abscess or total bilirubin greater than 3 times the upper limits of normal); anticipated survival period shorter than the study, symptoms of complicated appendicitis for less than 24 hours prior to current hospitalization; planned treatment of cIAI by staged abdominal repair; known or suspected inflammatory bowel disease or associated visceral abscess; received	**Primary Endpoint**: To demonstrate noninferiority in clinical response at the test-of-cure visit in the microbiological intent-to-treat population (for the FDA), modified intent-to-treat, and clinically evaluable populations. Clinical responses were categorized as clinical cure, clinical failure, or indeterminate/missing. • Microbiological ITT population: 86.8% clinical cure rate in eravacycline group and 87.6% clinical cure rate in ertapenem group with a difference of -0.8%. **Adverse Events**: Similar number of patients experienced treatment-emergent vomiting, anemia, pyrexia, and diarrhea in each treatment group. Adverse Event / Eravacycline / Ertapenem Nausea: 8.1% / 0.7% Phlebitis: 3% / 1.4% Severe Treatment-Emergent Adverse Events: 5.6% / 6%	**Author's Conclusion**: Eravacycline showed noninferiority to ertapenem for treatment of complicated intra-abdominal infections.

<table>
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<td>systemic antibiotics for their condition for more than 24 hours, received ertrapenem or any other carbapenem or tigecycline for the infection, and/or required systemic antimicrobial agents other than the study drugs.</td>
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<tr>
<td>IGNITE 4

Phase III, prospective, randomized, double-blind, multicenter trial to study the ervacycline compared to meropenem in treatment of cIAI.

N= 500 (250 in eravacycline group, 250 in meropenem group)

Noninferiority margin of 12.5%</td>
<td>Inclusion Criteria: 18 years and older, hospitalized for suspected cIAI, able to provide informed consent.

Exclusion Criteria: considered unlikely to survive the 6-8 week study, CrCl less than 50 mL/min, presence or possible signs of significant hepatic disease, immunocompromised condition, history of hypersensitivity to tetracyclines, carbapenems or beta-lactams, participation in any investigational drug or device study within 30 days of study entry, known or suspected nervous system disorder that suggests predisposition to seizures, and receipt of effective antibacterial drug therapy for cIAI for more than 24 hours in the 72 hours prior to randomization.</td>
<td>Primary Endpoint:
To demonstrate noninferiority in clinical cure rates at the test-of-cure visit in the microbiological intent-to-treat population.
• Microbiological ITT population: 90.8% clinical cure rate in eravacycline group and 91.2% clinical cure rate in meropenem group with a difference of -0.5%.

Secondary Endpoints:
Clinical cure rates in:
• Modified ITT population: 92.4% clinical cure rate in eravacycline group and 91.6% clinical cure rate in meropenem group with a difference of 0.8%.
• Clinically evaluable population: 96.9% clinical cure rate in eravacycline group and 96.1% clinical cure rate in meropenem group with a difference of 0.8%.

Adverse Events:
Treatment emergent adverse events occurred in 37.2% of patients in eravacycline group vs 30.9% of patients in the meropenem group.

<table>
<tr><th>Adverse Event</th><th>Eravacycline</th><th>Meropenem</th></tr>
<tr><td>Nausea</td><td>4.8%</td><td>0.8%</td></tr>
<tr><td>Vomiting</td><td>3.6%</td><td>2%</td></tr>
<tr><td>Phlebitis (infusion site)</td><td>3.2%</td><td>0.4%</td></tr>
<tr><td>Thrombosis (infusion site)</td><td>2.4%</td><td>0.4%</td></tr>
<tr><td>Wound infection</td><td>2.8%</td><td>1.6%</td></tr>
<tr><td>Diarrhea</td><td>2.4%</td><td>1.2%</td></tr>
</table>
</td>
<td>Author’s Conclusion:
Eravacycline was noninferior compared to meropenem in the treatment of adults with cIAI, including infections caused by resistant pathogens.</td>
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<tr>
<td>Omadacycline for Community-Acquired Bacterial Pneumonia

Phase III, randomized, double-blind,double-dummy, noninferiority trial.

N= 774 (386 in omadacycline group, 388 in moxifloxacin group)

Noninferiority margin of 10%</td>
<td>Inclusion Criteria: 18 years or older; three or more of the following four symptoms: cough, purulent sputum production, dyspnea, or pleuritic chest pain; two or more abnormal vital signs; one or more clinical sign or laboratory finding associated with community-acquired bacterial pneumonia; radiologically confirmed pneumonia; and were characterized as being in Pneumonia Severity Index (PSI) risk class II, III, or IV.

Exclusion Criteria: Received one or more doses of potentially effective systemic antibacterial treatment within 72 hours before the first dose of trial drug, had hospital-acquired pneumonia or empyema, had clinically significant liver or renal insufficiency, or were immunocompromised.</td>
<td>Primary Endpoint:
To demonstrate noninferiority in early clinical response assessed by investigators at 72 and 120 hours after the first dose of trial drug in the microbiologic ITT population.
• 81.1% early clinical response rate in omadacycline group and 82.7% clinical response rate in moxifloxacin group with a difference of -1.6%.

Secondary Endpoint:
Investigator-assessed clinical response at the post-treatment evaluation in the ITT population and the clinical per-protocol population.
• 87.6% clinical response rate in omadacycline group and 85.1% clinical response rate in moxifloxacin group with a difference of 2.5%.

Adverse Events:
Treatment emergent adverse events occurred in 41.1% of patients in omadacycline group vs 48.5% of patients in the moxifloxacin group.

<table>
<tr><th>Adverse Event</th><th>Omadacycline</th><th>Moxifloxacin</th></tr>
<tr><td>ALT Increased</td><td>3.7%</td><td>4.6%</td></tr>
<tr><td>Hypertension</td><td>3.4%</td><td>2.8%</td></tr>
<tr><td>γ-Glutamyltransferase increased</td><td>2.6%</td><td>2.1%</td></tr>
<tr><td>Insomnia</td><td>2.6%</td><td>2.1%</td></tr>
</table>
</td>
<td>Author’s Conclusion:
Omadacycline was noninferior compared to moxifloxacin for the treatment of community-acquired bacterial pneumonia in adults.</td>
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<tr><td></td><td></td><td>
<table>
<tr><td>Vomiting</td><td>2.6%</td><td>1.5%</td></tr>
<tr><td>Constipation</td><td>2.4%</td><td>1.5%</td></tr>
<tr><td>Nausea</td><td>2.4%</td><td>5.4%</td></tr>
<tr><td>AST Increased</td><td>2.1%</td><td>3.6%</td></tr>
<tr><td>Headache</td><td>2.1%</td><td>1.3%</td></tr>
<tr><td>Diarrhea</td><td>1%</td><td>8%</td></tr>
</table>
</td><td></td></tr>
<tr><td>A Randomized, Evaluator-Blind, Phase 2 Study Comparing the Safety and Efficacy of Omadacycline to Those of Linezolid for Treatment of Complicated Skin and Skin Structure Infections

Phase II, randomized, controlled, evaluator-blinded

N= 219 (111 in omadacycline group, 108 in linezolid group)</td><td>Inclusion Criteria: 18 years or older; one of four general categories of complicated skin and skin structure infections (cSSSI): wound infection, major abscess, infected ulcers in the lower extremity, or cellulitis; patients with diabetes mellitus or documented vascular insufficiency with infected ulcers of the lower extremity if the lesion was acutely infected and the ulcer was not present for more than three months; patients with cellulitis alone were eligible if they had diabetes mellitus or vascular insufficiency or if they received immunosuppressive therapy within a period of three months prior to developing cellulitis; received <48 hours of antibiotic therapy prior to enrollment or if they had received ≥48 hours of therapy and a resistant pathogen was identified.

Exclusion Criteria: Patients with erysipelas, cellulitis (but otherwise healthy), decubitus ulcers, infections considered life-threatening, infections potentially involving bone, or infections that were able to resolve with surgical intervention alone.</td><td>Primary Endpoint:
Compare the safety and tolerability of omadacycline to linezolid in patients with cSSSI.
• Treatment emergent adverse events occurred in 41.4% of patients in omadacycline group vs 50.9% of patients in the linezolid group.
• Treatment related adverse events occurred in 21.6% of patients in omadacycline group vs 30.6% of patients in the linezolid group.
• One serious adverse event was reported in an omadacycline-treated patient and two in a linezolid-treated patient.

Secondary Endpoints:
Rate of clinical response of omadacycline compared to linezolid for treatment of cSSSI.
• ITT: 88.3% for omadacycline group compared to 75.9% for linezolid group
• Modified ITT: 89.3% for omadacycline group compared to 75.6% for linezolid group
• Clinically evaluable: 98% for omadacycline group compared to 93.2% for linezolid group
• Microbiologically evaluable: 97.4% for omadacycline group compared to 93.7% for linezolid group

Adverse Events:
<table>
<tr><th>Adverse Event</th><th>Omadacycline</th><th>Linezolid (+/- aztreonam)</th></tr>
<tr><td>Nausea</td><td>11.7%</td><td>7.4%</td></tr>
<tr><td>Vomiting</td><td>4.5%</td><td>3.7%</td></tr>
<tr><td>Diarrhea</td><td>2.7%</td><td>5.6%</td></tr>
<tr><td>Constipation</td><td>4.5%</td><td>1.9%</td></tr>
<tr><td>Fatigue</td><td>4.5%</td><td>1.9%</td></tr>
<tr><td>ALT Increase</td><td>2.7%</td><td>6.5%</td></tr>
<tr><td>AST Increase</td><td>2.7%</td><td>4.6%</td></tr>
<tr><td>Dizziness</td><td>3.6%</td><td>4.6%</td></tr>
<tr><td>Headache</td><td>6.3%</td><td>8.3%</td></tr>
<tr><td>Rash/rash erythematous</td><td>4.5%</td><td>1.9%</td></tr>
</table>
</td><td>Author’s Conclusion:
Omadacycline was well tolerated and effective for treating patients with serious skin and soft tissue infections compared to linezolid.</td></tr>
<tr><td>Once-Daily Oral Sarecycline 1.5 mg/kg/day is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials

Phase III, randomized, double-blind, placebo-</td><td>Inclusion Criteria: aged 9-45 years old; weighed 33-136 kg; had 20-50 inflammatory lesions; ≤100 noninflammatory lesions; ≤2 nodules; and a score of 3 (moderate) or 4 (severe) on the Investigator’s Global Assessment (IGA) scale for inflammatory lesions of acne.

Exclusion Criteria: dermatologic condition; facial hair; any chronic illness interfering with study evaluations; allergy or resistance to tetracyclines; drug-induced acne; hormonal contraceptive initiation;</td><td>Primary Endpoint:
IGA success rate of sarecycline group compared to placebo group
• ITT population: IGA success rate was greater in the sarecycline group compared to the placebo group in both trials.
o SC1401
▪ Started at week 9 and continued through week 12
▪ 21.9% of sarecycline group achieved IGA success compared to 10.5% of placebo
o SC1402
▪ Started at week 6 and continued through week 12
▪ 22.6% of sarecycline group achieved IGA success compared to 15.3% of placebo

Safety
• SC1401:</td><td>Author’s Conclusion:
Sarecycline was effective, safe, and well tolerated for moderate to severe acne.</td></tr>
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<td>controlled, parallel-group, multicenter

SC1401 N= 968 (483 in sarecycline group, 485 in placebo group)
SC1402 N= 1034 (519 in sarecycline group, 515 in placebo group)</td>
<td>systemic retinoids; or systemic corticosteroids, androgens, or anti-androgens within 12 weeks prior to randomizations.</td>
<td>

Treatment emergent adverse events happened in 29.3% of patients in sarecycline group and 29.8% of patients in placebo group.
Treatment emergent adverse events considered to be related to study treatment were 1.9% in sarecycline group and 0.4% in placebo.

SC1402:

Treatment emergent adverse events happened in 25% of patients in sarecycline group and 26.7% of patients in placebo group.
Treatment emergent adverse events considered to be related to study treatment were 1.6% in sarecycline group and 0.6% in placebo.

Adverse Events:
<table>
<tr><th rowspan="2">Adverse Event</th><th colspan="2">SC1401</th><th colspan="2">SC1402</th></tr>
<tr><th>Sarecycline</th><th>Placebo</th><th>Sarecycline</th><th>Placebo</th></tr>
<tr><td>Nausea</td><td>4.6%</td><td>2.5%</td><td>1.9%</td><td>1%</td></tr>
<tr><td>Vomiting</td><td>2.1%</td><td>1.4%</td><td>0.6%</td><td>0.4%</td></tr>
<tr><td>Abdominal Pain</td><td>1.2%</td><td>1.2%</td><td>0.6%</td><td>0.2%</td></tr>
<tr><td>Abdominal Discomfort</td><td>1%</td><td>0.2%</td><td>0.4%</td><td>0.4%</td></tr>
<tr><td>Diarrhea</td><td>1%</td><td>1.7%</td><td>1.2%</td><td>1.2%</td></tr>
<tr><td>Dizziness</td><td>0.6%</td><td>1.4%</td><td>0.4%</td><td>0.8%</td></tr>
<tr><td>Motion Sickness</td><td>0%</td><td>0%</td><td>0.2%</td><td>0.2%</td></tr>
<tr><td>Photosensitivity</td><td>0%</td><td>0%</td><td>0.2%</td><td>0%</td></tr>
<tr><td>Sunburn</td><td>0.6%</td><td>0.4%</td><td>0.8%</td><td>0.2%</td></tr>
<tr><td>Vulvovaginal Candidiasis</td><td>1.1%</td><td>0%</td><td>0.3%</td><td>0%</td></tr>
<tr><td>Vulvovaginal Mycotic Infection</td><td>0.7%</td><td>0%</td><td>1%</td><td>0%</td></tr>
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Guideline	Recommendations
Diagnosis and Treatment of Adults with Community-Acquired Pneumonia: An official Practice Guidelines of the American Thoracic Society and Infectious Diseases Society of America 2019	• Empiric Treatment of Outpatients with CAP o No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*: doxycycline 100 mg twice daily o Comorbidities present: Amoxicillin/clavulanate or cephalosporin AND doxycycline 100 mg twice daily o Omadacycline needs further validation in the outpatient setting • Empiric Treatment of CAP in Inpatient Adults Without Risk Factors for MRSA and *Pseudomonas aeruginosa* o Contraindications present for macrolides and fluoroquinolones: Beta-lactam (ampicillin/sulbactam, cefotaxime, ceftaroline, or ceftriaxone) AND doxycycline 100 mg twice daily o In a single study, omadacycline was reported to be equivalent to moxifloxacin as monotherapy in adults with CAP. Omadacycline is effective in the presence of tetracycline resistance. Not recommended as a current treatment option due to less well-established safety information compared to current treatment recommendations.

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America	• MSSA SSTI (>8 years old)
	  ○ Doxycycline 100 mg twice daily
	  ○ Minocycline 100 mg twice daily
	• MRSA SSTI (>8 years old)
	  ○ Doxycycline 100 mg twice daily
	  ○ Minocycline 100 mg twice daily
	• Necrotizing infections of the skin, fascia, and muscle
	  ○ *Aeromonas hydrophila*
	  ▪ Doxycycline 100 mg IV every 12 hours AND ciprofloxacin or ceftriaxone
	  ○ *Vibrio vulnificus*
	  ▪ Doxycycline 100 mg IV every 12 hours AND ceftriaxone or cefotaxime
	• Animal or Human Bite Wounds
	  ○ Doxycycline 100 mg twice daily
	• Bacillary Angiomatosis and Cat Scratch Disease
	  ○ Doxycycline 100 mg twice daily for 2 weeks to 2 months

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report.	• Antibiotic for COPD exacerbation should be chosen based on local bacterial resistance patterns. • Empiric treatment includes aminopenicillin with clavulanic acid, macrolide, or tetracycline antibiotics.

Warnings, Precautions, and Adverse Effects[8-23]

Warnings/ Precautions

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
Pediatric: tissue hyperpigmentation, tooth enamel hypoplasia, permanent tooth discoloration when used during development of teeth in pregnancy, infancy and <8 y.o.	X	X	X	X	X	X	X
Pregnancy: avoid use in pregnancy due to reduced bone growth	X	X	X	X	X	X	X
Other							Boxed Warning: Treatment-related mortality*

**In a meta-analysis of Phase 3 and 4 clinical trials, patients treated with tigecycline were observed to have an increase in all-cause mortality compared to patients who were not treated with tigecycline. The cause has not been identified. Tigecycline should only be used when alternative treatments are not suitable.*

Adverse Reactions (>10%)

	Doxycycline	Eravacycline**	Minocycline	Omadacycline	Sarecycline***	Tetracycline*	Tigecycline
Anorexia			X				
Diarrhea							X
Erythema			X				

Headache			X				
Influenza	X						
Jarisch-Herxheimer Reaction	X						
Nausea			X	X			X
Vomiting			X	X			X

**Adverse reactions frequency not defined for tetracycline*
***None >10% for eravacycline – but nausea and infusion site reaction 8% and 7% respectively*
****None >10% for sarecycline – nausea 3%*

As a class, tetracycline antibiotics have a propensity to cause adverse GI effects, including nausea, vomiting, and abdominal discomfort or pain. These adverse reactions, most notably nausea and vomiting, are most severe with tigecycline, with upwards of 25% of patients affected. Both eravacycline and omadacycline have shown a much lower incidence of nausea and vomiting with rates typically <10%, and the majority of these treatment-related adverse effects seen in their clinical trials were classified as mild to moderate and did not result in drug discontinuation. Eravacycline has also been associated with infusion site reactions/phlebitis in as many as 8% of patients. Other class-wide effects of tetracyclines include discoloration of teeth and inhibition of bone growth in children as well as photosensitivity in all ages. Tetracyclines are also associated with hepatotoxicity in the form of increased transaminases, alkaline phosphatase, and total bilirubin; however, these effects are rare with an incidence typically <5%. Omadacycline and eravacycline appear to be better tolerated than tigecycline in this regard. As a class, tetracyclines are considered a very low risk of causing *Clostridium difficile*-associated diarrhea.

Interactions[16-23]

	Doxycycline	**Eravacycline**	**Minocycline**	**Omadacycline**	**Sarecycline**	**Tetracycline**	**Tigecycline**
***See list below**	X	X	X	X	X	X	X
Others					P-gp substrates**	Atovaquone, Lithium, Quinine	Dichlorphenamide, sodium picosulfate
Dairy Products	X	X	X	X	X	X	X

**Acitretin, antacids containing calcium, magnesium, aluminum, barbiturates, bismuth subsalicylate, calcium products, carbamazepine, cholestyramine, colesevelam, colestipol, digoxin, divalent or trivalent cations, hydantoin derivatives, isotretinoin, lanthanum carbonate, methotrexate, molindone, neuromuscular blocking agents, oral contraceptives, penicillins, photosensitizing agents, quinapril, rifampin, sucralfate, warfarin, and zinc salts. Strong CYP3A4 inducers: Phenobarbital, carbamazepine, rifampin, etc.*
****P-gp substrates: afatinib, betrixaban, colchicine, doxorubicin, lapatinib, loperamide, topotecan, etc.*

Tetracyclines have a number of well-described and clinically important drug-drug interactions. Divalent cations and sequestrants such as cholestyramine and colestipol can bind tetracyclines intraluminally and lead to reduced GI absorption. Anticonvulsant medications and strong CYP3A4 inducers can lead to decreased serum concentrations of the tetracycline agent. Omadacycline and tigecycline are similar to other tetracyclines in most of these effects, although they are not metabolized through the CYP system, and therefore not affected by the interactions mediated through that specific pathway. Eravacycline is metabolized by CYP3A4 and so has a drug interaction profile more similar to traditional tetracyclines.

Dosage and Administration[8-15]
Dose Adjustments

	Doxycycline	**Eravacycline**	**Minocycline**	**Omadacycline**	**Sarecycline**	**Tetracycline**	**Tigecycline**

Typical Dosing	100 mg q12h	1 mg/kg q12h	200 mg x 1, followed by 100 mg q12h	IV: 200 mg x 1 dose, followed by 100 mg q24h PO: 450 mg once daily on Days 1 and 2, followed by 300 mg q24h	33 to 54 kg: 60 mg q24h 55 to 84 kg: 100 mg q24h 85 to 136 kg: 150 mg q24h	250 mg q6h	100 mg x 1 dose, followed by 50 mg q12h
Geriatric	None	None	None	None	None	None	None
Pediatric (≥8 years old)	2.2 mg/kg/dose every 12 hours. Max of 200 mg/day	No dosing information provided	Oral IR and IV: 4 mg/kg once (max dose 200mg) then 2 mg/kg/dose every 12 hours (Oral max100 mg/dose and IV max of 400 mg/day)	No dosing information provided	33 to <55 kg: 60 mg once daily 55 to <85 kg: 100 mg once daily 85 to 136 kg: 150 mg once daily	25-50 mg/kg/day in divided doses every 6 hours	Reserve for when no effective alternative therapy available. Dose adjustments based on child's age**
Renal Dose Adjustment	None	None	Oral IR and IV: CrCl <80 ml/min do not exceed 200 mg/day	None	None	Decrease dose or extend doing interval	None
Hepatic Dose Adjustment	None	Severe impairment (Child-Pugh class C): 1 mg/kg every 12 hours on day 1, then 1 mg/kg every 24 hours	None	None	None	No	Severe impairment (Child class C): initial 100 mg dose once, then 25 mg every 12 hours

LD = loading dose, MD = maintenance dose
***<8 years receive LD: 1.5-3 mg/kg once and MD: 1-2 mg/kg every 12 hours, max 50 mg/dose; 8-11 years receive 1.2 to 2 mg/kg/dose, max 50 mg/dose; ≥12 years receive 50 mg every 12 hours*

Monitoring Parameters[8-15]

	Doxycycline	Eravacycline	Minocycline	Omadacycline	Sarecycline	Tetracycline	Tigecycline
CBC	X					X	
LFTs	X	X	X	X		X	X
Renal Function Tests	X	X	X	X		X	
Others	Test of cure for STI follow-up	Signs and symptoms of anaphylaxis during administration	Test of cure for STI follow-up		Ophthalmologic evaluation with visual changes		Signs and symptoms of anaphylaxis during administration

Susceptibility Testing

Susceptibility testing capabilities for the newer tetracyclines are variable at this time. For Enterobacteriales and Acinetobacter, activity for omadacycline and eravacycline can be inferred if tigecycline susceptibility is confirmed via Microscan. If specific testing is necessary, omadacycline E-test strips are available for clinical use and have been validated by the microbiology laboratory. There are commercially available E-test strips and Kirby-Bauer disks for testing eravacycline, although these have not been validated in the microbiology laboratory to this point. FDA Susceptibility Interpretive Criteria are available for both omadacycline and eravacycline; CLSI interpretive criteria are not yet available:

Eravacycline - https://www.fda.gov/drugs/development-resources/eravacycline-injection-products
Omadacycline - https://www.fda.gov/drugs/development-resources/omadacycline-injection-and-oral-products

How Supplied/Cost[8-15]

	Doxycycline	**Eravacycline**	**Minocycline**	**Omadacycline**	**Sarecycline**	**Tetracycline**	**Tigecycline**
Brand name	Vibramycin	Xerava	Minocin	Nuzyra	Seysara	Off-market: Panmycin, Sumycin	Tygacil
Formulations available (route)	Oral: capsule, tablet, suspension, syrup IV solution	IV solution	Oral: capsule, tablet IV solution	Oral: tablet IV solution	Oral: tablet	Oral: capsule	IV solution
Cost ($ per unit)	**50 mg** Capsule: 0.20 **100 mg** Tablet: 0.15 Capsule: 0.18 Vial: 18.78	**50 mg** Vial: 49.00	**50 mg** Tablet: 1.81 Capsule: 0.18 **75 mg** Tablet: 2.12 **100 mg** Tablet: 3.44 Capsule: 0.37 Vial: 179.88	**100 mg** Vial: 317.4 **150 mg** Tablet: 181.70	**100 mg** Tablet: 28.30	**250 mg** Capsule: 1.55 **500 mg** Capsule: 2.91	**50 mg** Vial: 40.00
Cost per day (based on maintenance dosing)	IV: $37.56 PO: $0.30	$196.00	IV: $359.76 PO: $0.74	IV: $317.40 PO: $362.00	$28.30	$6.20	$80.00
Administration Instructions	IV: Infuse over 1-4 hours Oral: Adequate fluids, empty stomach, 1 hour before or 2 hours after meals, 1-2 hours before or 4 hours after certain meds*	Infuse over 60 minutes via dedicated line or Y-site. If IV line used for multiple drugs, then flush line before and after eravacycline.	IV: infuse over 60 minutes Oral: Adequate fluids, with or without food, separate administration from certain medications*	Infuse 200 mg over 60 minutes, 100 mg over 30 minutes via dedicated line or Y-site. If IV line used for multiple drugs, then flush line before and after omadacycline.	Adequate fluids, with or without food, separate administration from certain medications*	Adequate fluids, empty stomach, 1 hour before or 2 hours after meals, 1-2 hours before or 4 hours after certain medications*	Infuse over 30-60 minutes via dedicated line or Y-site. If IV line used for multiple drugs, then flush line before and after tigecycline.
Storage: Tablets	68-77 °F		IR: 68-77 °F ER: 59-86 °F	68-77 °F	68-77 °F	68-77°F	

Capsules	<86 °F		68-77 °F				
IV Solution	Intact vials 68-77 °F	Intact vials 36-46 °F; Diluted solution ≤77 °F up to 24 hours or 36-46 °F up to 7 days	Intact vials 68-77 °F; Diluted solution ≤77 °F up to 4 hours or 36-46 °F up to 24 hours	Intact vials 68-77 °F; Diluted solutions ≤77 °F up to 12 hours or 36-46 °F up to 7 days			Intact vials 68-77 °F; diluted 36-46 °F for up to 48 hours

** Antacids, iron products, bismuth subsalicylate, calcium-containing products, magnesium containing products*

Inpatient Utilization at Nebraska Medicine

Drug Name	Inpatient Cases
Doxycycline	885
Minocycline	24
Omadacycline	1
Tetracycline	1
Tigecycline	6

**Number of patients treated with specific tetracycline antibiotic in 2019*

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References

1. May DB. Tetracyclines. In: Mitty J, ed. *UpToDate*. Waltham, Mass.: UpToDate, 2020. www.uptodate.com. Accessed March 2, 2020.
2. Speer BS, Shoemaker NB, Salyers AA. Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clin Microbiol Rev*. 1992; 5(4):387-399.
3. Stein GE, Craig, WA. Tigecycline: a critical analysis. *Clin Infect Dis*. 2006; 43(4): 518-524.
4. 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 (IGNITE1) trial: a randomized clinical trial. *JAMA Surg*. 2017; 152(3):224-232.
5. Seifert H, Stefanik D, Sutcliffe J, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. *Int J Antimicrob Agents*. 2018; 51(1):62-64.
6. Stets R, Popescu M, Gonong JR, et al. Omadacycline for community-acquired bacterial pneumonia. *N Engl J Med*. 2019; 380(6):517-527.
7. Noel GJ, Draper MP, Hait H, et al. A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. *Antimicrob Agents Chemother*. 2012; 56(11):5650-5654.
8. Doxycycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.;[updated 03/02/2020; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=doxycycline&t=name&va=doxycycline.
9. Demeclocycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.;[updated 01/30/2020; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=demecloxycline&t=name&va=demecloxycline.
10. Eravacycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.;[updated 11/21/2019; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=eravacycline&t=name&va=eravacycline.

11. Minocycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.:;[updated 02/29/2020; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=minocycline&t=name&va=minocycline.
12. Omadacycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.:;[updated 02/19/2020; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=omadacycline&t=name&va=omadacycline.
13. Sarecycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.:;[updated 02/01/2020; accessed 03/03/2020]. https://online.lexi.com/lco/action/search?q=sarecycline&t=name&va=sarecycline.
14. Tetracycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.:;[updated 03/04/2020; accessed 03/04/2020]. https://online.lexi.com/lco/action/search?q=tetracycline&t=name&va=tetracycline.
15. Tigecycline. In: Lexi-Drugs Online. Hudson (OH): Lexi-Comp, Inc.:;[updated 03/06/2020; accessed 03/06/2020]. https://online.lexi.com/lco/action/search?q=tigecycline&t=name&va=tigecycline.
16. Doxycycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/07/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=212&n=Doxycycline&t=0&enh=1.
17. Demeclocycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/17/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=171&n=Demeclocycline&t=0.
18. Eravacycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/17/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=5095&n=Eravacycline&t=0.
19. Minocycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 02/05/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=407&n=Minocycline&t=0.
20. Omadacycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/17/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=5105&n=Omadacycline&t=0.
21. Sarecycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/17/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=5104&n=Sarecycline&t=0.
22. Tetracycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/17/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=598&n=Tetracycline&t=0.
23. Tigecycline. In: Clinical Pharmacology. Tampa (FL): Gold Standard. [updated 01/21/2020; accessed 03/03/2020]. http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=3367&n=Tigecycline&t=0.
24. 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 intraabdominal infections. *Clin Infect Dis*. 2019; 69(6):921-929.
25. Moore A, et al. Once-daily oral sarecycline 1.5 mg/kg/day is effective for moderate to severe acne vulgaris: results from two identically designed, phase 3, randomized, double-blind clinical trials. *J Drugs Dermatol*. 2018; 17(9):987-996.
26. Metlay JP, et al. Diagnosis and Treatment of Adults with Community-Acquired Pneumonia: An official Practice Guidelines of the American Thoracic Society and Infectious Diseases Society of America 2019. *Am J Respir Crit Care Med*. 2019; 200(7):e45-67.
27. Stevens DL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014; 59(2):e10-52.
28. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2020 Report. https://goldcopd.org/gold-reports/. Accessed March 12, 2020.