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Drug Class Update with New Drug Evaluation: Oral Tetracyclines

Date of Review: March 2019
Generic Name: omadacycline
sarecycline

End Date of Literature Search: 11/26/2018
Brand Name (Manufacturer): Nuzyra™ (Paratek Pharmaceuticals, Inc.
Seysara™ (Allergan Pharmaceuticals, Inc.)
Dossier Received: Yes / No

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The tetracycline class has had two new drug approvals, omadacycline and sarecycline, since the last review in May of 2017. The purpose of this review is to evaluate the data related to the new tetracycline antibiotics and any additional new comparative efficacy or harms data published for the tetracycline class since the last review.

Research Questions:
1. Is there any new comparative evidence for antibiotics in the tetracycline class for clinically important outcomes such as mortality, hospitalizations, clinical clearance, and re-infection?
2. Is there any new comparative evidence evaluating harms for antibiotics in the tetracycline class?
3. Are there subpopulations of patients for which specific tetracycline antibiotics may be more effective or associated with less harm?
4. What is the evidence for efficacy and harms for the new tetracycline antibiotics, omadacycline and sarecycline?

Conclusions:
- Three guidelines, one systematic review and three randomized clinical trials provided evidence for the tetracycline class review.
- The National Institute of Health and Care Excellence (NICE) guideline recommendations are:
  - Doxycycline first-line for the treatment of an acute exacerbation of chronic obstructive pulmonary disease (COPD)[1]
  - Doxycycline as an alternative treatment option in patients requiring antibiotics for acute sinusitis[2]
  - Doxycycline as first-line treatment in patients 9 years and older with Lyme disease[3]

Efficacy
- Cochrane found moderate quality evidence of higher clinical cure rates with azithromycin compared to doxycycline for patients with mild to moderate pelvic inflammatory disease (PID), 85% versus 63%, (relative risk [RR] 1.35; 95% confidence interval [CI], 1.10 to 1.67; P<0.05/number needed to benefit [NNTB] 5).[4]

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- There is insufficient evidence to support superior efficacy or safety of the new tetracycline antibiotics, omadacycline and sarecycline, over currently preferred therapies.[5–7]
- There is insufficient evidence on the use of tetracycline antibiotics in specific subgroups of patients.

Safety
- There is insufficient evidence demonstrating differences in harms between antibiotics used for the treatment of acute COPD exacerbations.

Recommendations:
- No changes to the preferred drug list are recommended.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- There was no evidence of differences in comparative efficacy/effectiveness or safety between the antibiotics in the tetracycline class based on the previous review in May of 2017. A policy review at this time found insufficient evidence for the use of tetracyclines beyond 14 days, with the exception of the diagnosis of acne fulminans, severe cystic acne (coverage starting in 2020), and rosacea, which is unfunded. In response to the review, the use of tetracycline antibiotics beyond 14 days, for two separate claims, every 3 months requires prior authorization (Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes) to ensure use for an Oregon Health Plan (OHP) funded condition. Preferred drugs in the class include doxycycline and tetracycline.

Background:
The tetracycline class consists of five, broad spectrum antibiotics (**Table 1**).[8] Tetracyclines exhibit a bacteriostatic effect by inhibiting protein synthesis. The spectrum of activity for tetracyclines include aerobic-gram positive and gram-negative bacteria, as well as atypical pathogens. Doxycycline is most commonly used clinically due to twice daily dosing, tolerability, broad spectrum of activity and the availability of oral and intravenous (IV) dosage forms. Some of the common indications for tetracyclines include: acne, rosacea, sexually transmitted diseases, respiratory tract infections, acute bacterial skin structure infections (ABSS), and urinary tract infections (UTI).[8] In addition, doxycycline is indicated for the treatment of moderate to severe purulent skin infections for empiric treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Tetracyclines are commonly given for short durations, up to 14 days, with the exception of treatment for vertebral osteomyelitis and bone and joint infections, and certain dermatological conditions (e.g., acne fulminans, severe cystic acne).[9]

Antibacterial resistance to tetracyclines has been demonstrated. Resistance develops by preventing accumulation of the drug inside the cell, and resistance to one drug in the class often confers resistance to the entire class. The newly approved omadacycline has been shown to have activity against some bacteria that are resistant to doxycycline and minocycline.[10]

Table 1. Tetracycline Antibiotics[8,10,11]

Drug	Route	Comments
Tetracycline	Oral	Twice daily to four-times daily dosing
Doxycycline	Oral/IV	Administer without regard to food; twice daily dosing
Minocycline	Oral	Used for acne, not usually first-line
Omadacycline	Oral/IV	Requires loading dose; available in IV and oral formulation

Sarecycline	Oral	Approved for non-nodular moderate to severe acne only

Abbreviations: IV = intravenous

Tetracyclines should not be administered with multivalent cations (e.g., calcium, aluminum, iron, magnesium) which have been shown to inhibit the absorption. Tetracyclines should not be given to children under the age of eight due to the potential of permanent tooth discoloration, with the exception of doxycycline which can be used in any age child if absolutely necessary for short durations.[8] The most common adverse effects of the tetracycline class are: gastrointestinal upset, photosensitivity and tooth discoloration (young children).

The main outcomes of importance in patients using tetracycline antibiotics are: mortality, hospitalization, re-infection, number of acne lesions and clinical cure. Reduction in exacerbations is an important outcome in patients with COPD receiving antibiotics (e.g., pneumonia).

Ninety-eight percent of tetracycline claims are for the preferred agent doxycycline. Overall the tetracycline class represents a small source of health care utilization for Oregon Health Plan (OHP) fee-for-service (FFS) patients.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

<u>Cochrane – Antibiotic Therapy for Pelvic Inflammatory Disease</u>

A 2017 Cochrane review evaluated the comparative efficacy of antibiotics to treat PID among women.[4] Thirty-seven trials of women 14 years and older with a diagnosis of PID (based on Centers for Disease Control criteria) were identified and included the following antibiotics: clindamycin, doxycycline, azithromycin, quinolones, cephalosporins, nitroimidazoles, and aminoglycosides.[4] Many of the eligible studies had an unclear risk of bias, partly due to clinical trial completion before 2000 with inferior study designs. Selective reporting and unclear allocation concealment led to unclear risk of bias. Funnel plot analysis indicated some degree of publication bias. Women were divided into groups based on PID severity; mild-moderate (e.g., absence of tubo-ovarian abscess) and severe (e.g., systemically unwell, presence of tubo-ovarian abscess). Patients from inpatient and outpatient settings were included. Primary outcomes of interest were clinical cure (time to resolution of signs and symptoms of PID as determined by the provider) and adverse events.

In an analysis of two trials comparing azithromycin to doxycycline, there was no statistically significant difference in clinical cure rates for mild to moderate PID, 82% and 69% (RR 1.18; 95% CI, 0.89 to 1.55; p>0.05).[4] However, restricting the analysis to studies with low risk of bias found moderate strength of evidence (one

RCT) that azithromycin had a higher rate of clinical cure compared to doxycycline in patients with mild to moderate PID, 85% versus 63% (RR 1.35; 95% CI, 1.10 to 1.67; P<0.05; NNTB 5). For severe PID, doxycycline was similar to azithromycin based on low quality evidence (RR 1.0; 95% CI, 0.96 to 1.05). Adverse events were also similar between comparators.[4]

After review, four systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), insufficient or low quality evidence or outcome studied (e.g., non-clinical).[12–15]

New Guidelines:

NICE – Chronic Obstructive Pulmonary Disease (acute exacerbation): Antimicrobial Prescribing

A 2018 guideline on managing acute exacerbations of COPD as it relates to antimicrobial prescribing was published by NICE. Acute exacerbations can be triggered by multiple causes and approximately half have bacterial etiology. Evidence for recommendations were from a systematic review and meta-analysis of randomized controlled trials which included antibiotic treatment (including doxycycline) durations of 5 to 14 days.[1] Moderate quality evidence found antibiotic treatment in patients with an acute exacerbation of COPD reduced the number of patients with a subsequent exacerbation (didn't resolve or improve up to 1 month after treatment) compared to placebo, 29.4% versus 36.1% (NNT 15).[1] Patients with more severe infections, based on treatment setting, benefited the most from antibiotic treatment. Moderate quality evidence found no significant difference in all-cause mortality (1.0% vs. 1.6%; 95% CI, 0.27 to 1.63; p>0.05). Limitations to the evidence used for treatment recommendations is that studies often included patients with varying severity of acute exacerbations and the diagnosis of an acute exacerbation is variable from study to study.

When treating exacerbations, the following considerations should be taken: severity of symptoms, need for inpatient treatment, previous exacerbations/hospitalizations, previous sputum cultures and susceptibility results, and the risk of antimicrobial resistance with repeated courses of antibiotics.[1] Consideration should be taken to have susceptibility analysis done on sputum cultures and switch antibiotics if resistance is present and symptoms are not improving. Antibiotic treatment recommendations are presented in **Table 2**. Patients that are receiving prophylactic antibiotics should receive antibiotics for acute treatment from a different antibiotic class. Doxycycline is recommended as a first line treatment for COPD exacerbations.

Table 2. Antibiotic Treatment for Acute Exacerbations of COPD in Adults (18 years and older)[1]

Antibiotic	Dosage
*First Line Treatment**	
Amoxicillin	500 mg three times daily for 5 days
Doxycycline	200 mg on first day, then 100 mg once a day for 5-day course in total
Clarithromycin	500 mg twice a day for 5 days
Second-line Treatment	
Use alternative first-choice option from a different class	See above
*Second-line Treatment if Patient is at High Risk of Treatment Failure^*	
Amoxicillin/clavulanic acid	500/125 mg three times daily for 5 days
Levofloxacin	500 mg once a day for 5 days
Sulfamethoxazole and trimethoprim	960 mg twice a day for 5 days

First-line Intravenous Antibiotic†	
Amoxicillin	500 mg three times a day‡
Amoxicillin/clavulanic acid	1.2 grams three times daily‡
Clarithromycin	500 mg two times a day
Sulfamethoxazole and trimethoprim	960 mg twice a day (based on trimethoprim component)
Piperacillin with tazobactam	4.5 grams three times a day
Second-choice Intravenous Antibiotic	
Consult local microbiologist: guided by susceptibilities	
Key: * Empirical treatment or guided by sputum cultures, † Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible, ^ Patients considered at high risk of treatment failure if they have had repeated courses of antibiotics, a previous or current sputum culture with resistant bacteria or a higher risk of developing complications, ‡ Not available as an intravenous solution in the US	

Safety

Common adverse reaction for antibiotics in general include diarrhea in 2% to 25% of patients and low quality evidence found the incidence of adverse events was higher with antibiotics compared to placebo, 10.6% versus 7.4%.[1] There was no difference found between different antibiotics or classes of antibiotics in the risk of adverse events.

NICE – Sinusitis (acute): antimicrobial prescribing

NICE released guidance on the use of antibiotics in patients with sinusitis.[2] Often patients improve without the use of antibiotics and withholding antibiotics rarely leads to complications. Moderate quality of evidence found increased cure rates with antibiotics compared to placebo (NNT 7-21).[3] A back-up antibiotic prescription is recommended for patients if symptoms do not improve within 7 days or if symptoms worsen abruptly or increase in severity. Patients should be treated when presenting with symptoms if they are systemically unwell, have signs or symptoms of a more serious illness or are at high risk of complications. Doxycycline is recommended as an alternative first-line treatment for those patients with sinusitis and a penicillin allergy or intolerance, for both adults and those 12-17 years old.

Safety

Antibiotics are associated with more adverse reactions compared to placebo with a number needed to harm (NNH) of 8-11.[2] Diarrhea was found to more common with antibiotic therapy compared to placebo with a NNH of 18.

NICE – Lyme Disease

The National Institute for Health and Care Excellence released a guideline on the treatment of Lyme disease in 2018.[3] Antibiotics are recommended for patients who are diagnosed with Lyme disease. The route and type of antibiotic are symptom dependent. Oral doxycycline for 21 days is recommended first line in adults and in children over the age of 9 years. The exception is in patients that have Lyme disease affecting the central nervous system and for those with Lyme carditis and are hemodynamically unstable, in which intravenous ceftriaxone is recommended first line. Alternative treatment options include amoxicillin or azithromycin. For patients who are 12 and under the recommendations are divided by age: 9-12 years and under 9.[3] In children 9-12 years oral doxycycline is recommended for 21 days, with amoxicillin or azithromycin as alternatives. In patients under 9 years, amoxicillin is recommended with azithromycin as an

alternative. The exception is the same as for adults in that for those patients with Lyme disease affecting the central nervous system or those with Lyme carditis and are hemodynamically unstable, IV ceftriaxone is recommended regardless of age. A second course of antibiotics should be considered in patients with ongoing symptoms.

New Formulations or Indications:
Minocycline (Minolira®) – a new extended-release (ER) formulation of minocycline was approved in May of 2017 for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients in 12 years and older.[16] Minocycline ER was studied in two, 12 week, placebo-controlled studies which demonstrated mean improvement in inflammatory lesions compared to placebo by 11.4% more in study 1 and 15% more in study 2 (p-values not provided).[16]

Doxycycline (Xyrosa®) - a new formulation of doxycycline was approved for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients in April of 2017.[17] Prescribing information is not available.

Doxycycline (Lymepak®) – doxycycline is used off-label for the treatment of Lyme disease. A new packaging system containing doxycycline tablets has been approved for use in patients, eight years and older weighing 45 kg or more, with early Lyme disease (as evidenced by erythema migrans) due to *Borrelia burgdorferi*.[18] Clinical efficacy evidence was derived from previous trials evaluating doxycycline use in children and adults with Lyme disease. Lymepak is available in blister cards containing 14 tablets of doxycycline 100 mg, to be taken every 12 hours for a total of 21 days.[18]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Doxycycline[19]	Acticlate	November 2017	Warnings and precautions	Severe skin reactions (e.g., exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) and drug reaction with eosinophilia and systemic symptoms (DRESS). Discontinue doxycycline if skin reactions occur.
Doxycycline[19]	Acticlate	November 2017	Adverse reactions	Superficial discoloration of adult permanent dentition, reversible upon discontinuation. Permanent discoloration and enamel hypoplasia may occur when used during tooth development.

Randomized Controlled Trials:
A total of 20 citations were manually reviewed from the initial literature search. After further review, 17 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The included studies are available in Table 6 and 8.

NEW DRUG EVALUATION: Omadacycline

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Omadacycline is a tetracycline antibiotic indicated for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin structure infections (ABSSI) in adults that are infected with susceptible organisms.[10] Omadacycline is classified as an aminomethylcycline antibacterial within the tetracycline class which exhibits bacteriostatic activity, with the exception of having bactericidal activity against some isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae*, by binding to the 30S ribosomal subunit and inhibiting protein synthesis. Omadacycline is one of the few oral antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[20]

Three (1 in CABP and 2 in ABSSI), phase 3, double-blind, double-dummy randomized controlled, noninferiority trials provided evidence for approval (OPTIC, OASIS-1 and OASIS-2).[5,6,10,21] In two of the trials (OPTIC and OASIS-1), patients received intravenous (IV) loading doses followed with oral therapy, with the total treatment duration lasting 7-14 days in all trials. The primary endpoint for the CABP trial was early clinical response (ECR) (survival with improvement in at least 2 of 4 symptoms, which include cough, sputum production, chest pain, dyspnea without rescue antibiotics) at 72-120 hours following the first dose.[5] The primary endpoint for the studies evaluating omadacycline in ABSSI was early clinical response (ECR) (survival with a reduction in lesion size of at least 20% without rescue antibacterial therapy) at 48-72 hours after the first dose.[6,10] The noninferiority margin was set at 10% for all trials based on the modified intent to treat (mITT) population.

In the OPTIC trial, included patients had CABP, were hospitalized, mean age of 62 years old, 55% male, and Pneumonia Severity Index (PSI) risk II-IV.[5,19] The PSI is a I-V classification of risk of death, with higher numbers indicating more risk. Omadacycline 100 mg IV every 12 hours for 2 doses on day 1, followed by 100 mg IV daily for 3 days or more, then 300 mg orally once daily was compared to moxifloxacin 400 mg which was given IV for 3 or more days and then 400 mg orally.[5] Clinical success at the ECR time point occurred in 81.1% of patients treated with omadacycline and 82.7% treated with moxifloxacin (mean difference [MD] -1.6%; -7.1 to 3.8)(Table 6).[5] Patients with risk factors indicating a higher severity of illness (e.g., age 65 or older, chronic lung disease, diabetes) demonstrated lower clinical success rates when treated with omadacycline compared to moxifloxacin. At post therapy evaluations clinical response rates for omadacycline were the highest for the following organisms (baseline pathogen): *Streptococcus pneumonia* (86%), *Methicillin-susceptible Staphylococcus aureus* (MSSA) (72.7%), *Haemophilus influenzae* (81.3%), *Haemophilus parainfluenzae* (83.3*%), Klebsiella pneumonia* (76.9%), *Legionella pneumophila* (93.1%), *Mycoplasma pneumoniae* (88.6%), and *Chlamydophila pneumoniae* (93.3%).[5,19]

Patients included in the first ABSSSI trial, OASIS-1, were 44-47 years and a majority were male (63-65%). Patients were treated for 7-14 days of omadacycline or linezolid.[6] Pathogen diagnosis were as follows: cellulitis (38%), wound infection (33%), and major abscess (29%). Patients were randomized to omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV daily for 3 or more days, then transitioned to oral omadacycline 300 mg daily if possible, or linezolid 600 mg IV every 12 hours for 3 or more days then switching to 600 mg every 12 hours orally if possible. Clinical success was 84.8% with omadacycline compared to 85.5% with linezolid (MD -0.7%; 95% CI, -6.3 to 4.9)(**Table 6**).[6] Clinical response at the post-treatment evaluation for baseline pathogens were as follows: *Staphylococcus aureus* (methicillin-susceptible) (84%), *Staphylococcus aureus* (methicillin-resistant) (83%), *Streptococcus anginosus group* (74%), *Streptococcus pyogenes* (73%) and *Enterococcus faecalis* (90%).[20] Pooled clinical response from both ABSSSI studies based on type of infection are presented in **Table 4**.[21]

In the second trial, OPTIC-2 (not published), patients with ABSSSI were given omadacycline 450 mg orally on day 1 and day 2 followed by 300 mg orally once daily was compared to linezolid 600 mg every 12 hours. Patients had the following infections: wound infections (58%), cellulitis (24%), and major abscess (18%). The clinical ECR was 87.3% in patients receiving omadacycline and 82.2% in patients receiving linezolid (MD 5.1%; 95% CI, -0.2 to 10.5).[10] Pooled clinical response from both ABSSSI studies based on type of infection are presented in **Table 4**.[21]

Table 4. Early Clinical Response based on Wound Infection Type Pooled for both ABSSI studies (mITT population)[21]

Clinical Success Rate	Omadacycline	Linezolid	Difference vs. Linezolid
Cellulitis/erysipelas	165 (78.9%)	164 (83.9%)	-2.2 (95% CI, -10.0 to 5.5)
Wound infection	278 (89.1%)	269 (88.5%)	4.5 (95% CI, -0.8 to 9.9)
Major Abscess	140 (90.3%)	130 (84.3%)	4.2 (95% CI, -3.1 to 11.8)

Noninferiority was demonstrated in all three trials.[5,6,10]

Limitations to the evidence include: lack of long-term trial data, analysis of mITT population in a trial with a noninferiority design which could bias the results to show no difference between treatments; however, post-hoc analysis of per-protocol population confirmed noninferiority of omadacycline to moxifloxacin and omadacycline to linezolid.[19,20] Evaluating the data based on the per protocol population is preferred for noninferiority trials. There is insufficient data to show superiority of omadacycline compared to moxifloxacin, and there may be an increased risk of mortality associated with therapy.

Clinical Safety:

Common adverse events associated with omadacycline include nausea, vomiting and infusion site reactions. Other adverse events occurring in 2% or greater patients include the following: alanine aminotransferase increases, aspartate aminotransferase increases, gamma-glutamyl transferase increases, hypertension, headache, diarrhea, insomnia, and constipation.[10] An imbalance in the mortality rates between omadacycline and moxifloxacin (2% versus 1%, respectively) was demonstrated in patients with CABP without a known etiology.[10,20] Use with caution in patients at increased risk of mortality. An additional trial will be required to further evaluate this finding. Use of omadacycline in pregnancy and childhood may cause tooth discoloration and enamel hypoplasia as well as inhibition of bone growth. Discontinue omadacycline if *Clostridium difficile* Associated Diarrhea (CAD) occurs. In the ABSSI trials discontinuations due to adverse events was 1.6% to 1.8% in the omadacycline group and 1.1% to 2.1% in the linezolid group.[21]

Table 5. Pharmacology and Pharmacokinetic Properties of Omadacycline[10]

Parameter	
Mechanism of Action	Aminomethylcycline antibacterial within the tetracycline class of antibacterial drugs
Oral Bioavailability	34.5% following single 300 mg dose
Distribution and Protein Binding	23.6 to 25.6 Liters 20% protein bound
Elimination	14.4% urine and 77.5% to 84.0% feces
Half-Life	8.1 to 10.7 hours oral and 21.7 hours IV
Metabolism	Not metabolized

Abbreviations: IV - intravenous

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Infection resolution
2) Mortality
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Early clinical response (see Table 6)

Table 6. Comparative Evidence Table for Omadacycline.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Stets, et al[5] Phase 3, DB, DD, RCT, NI (OPTIC)	1. Omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV every 24 hours (O)* 2. Moxifloxacin 400 mg IV every 24 hours (M)* * A transition to oral omadacycline 300 mg every 24 hours or oral moxifloxacin 400 mg every 24 hours was allowed after 3 days Total treatment: 7-14 days	Demographics: Age (mean): 62 yrs Male: 55% Current smoker: 24% Mild to moderate COPD: 54% Asthma: 5% PSI score: 84 Key Inclusion Criteria: - 18 years or older - ≥ 3 of the following: cough, purulent sputum production, dyspnea, or pleuritic chest pain - ≥ 2 abnormal vital signs - ≥ 1 clinical sign or laboratory finding associated with CABP - radiologically confirmed pneumonia - Pneumonia severity index class II-IV Key Exclusion Criteria:	mITT: 1. 386 2. 388 PP: 1. 340 2. 345 Attrition: 1. 12% 2. 11%	Early Clinical Response (mITT population)†: O: 313 (81.1%) M: 321 (82.7%) MD -1.6% (95% CI, -7.1 to 3.8) *Noninferior to moxifloxacin* Early Clinical Response (per-protocol population/post-hoc analysis)†: O: 308 (86.5%) M: 314 (87.2%) MD -0.7 (95% CI, -5.7 to 4.3) Secondary Endpoints: Clinical response at post-treatment evaluation (5 to 10 days after last dose): O: 338 (87.6%) M: 330 (85.1%) MD 2.5% (95% CI, -2.4 to 7.4)	NA for all	ALT increased: O: 14 (3.7%) M: 18 (4.6%) Hypertension: O: 13 (3.4%) M: 11 (2.8%) Discontinuations due to adverse events: O: 21 (5.5%) M: 27 (7.0%) Serious Adverse Events: O: 23 (6%) M: 26 (6.7%) Death: O: 8 (2.1%) M: 4 (1.0%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized in a 1:1 ratio via an interactive voice response/interactive web response system. Performance Bias: (low) double-blind design and trial personal were blinded to treatment assignment. Detection Bias: (high) data analysis done by manufacturer. Attrition Bias: (high) Over 10% attrition in both groups. Analysis done on mITT population. Reporting Bias: (low) Outcomes reported as prespecified. Other Bias: (high) Industry funded. **Applicability**: Patient: In patients with community acquired bacterial pneumonia. More patients in the omadacycline group compared to moxifoxacin were current smokers, 27% vs. 21%, and more patients had COPD, 57% vs. 51%. Intervention: Omadacycline dose was appropriate. Comparator: Comparison to another first-line treatment for pneumonia would be more informative than a moxifloxacin comparison,

		- One or more doses of potentially effective systemic antibacterial treatment within 72 hours of the first dose - history of hospital-acquired pneumonia or empyema - clinically significant renal or hepatic insufficiency - immunocompromised patients						which is not recommended first or second line by guidelines. Outcomes: Clinical response to therapy is an appropriate outcome. Setting: Multi-center study in 86 sites in Europe, North America, South America, the Middle East, Africa and Asia.
O'Riordan, et al[6] (OASIS-1) Phase 3, DB, DD, RCT, NI	1. Omadacycline 100 mg IV every 12 hours for 2 doses then 100 mg IV every 24 hours (O)* 2. Linezolid 600 mg IV every 12 hours (L)* * A transition to oral omadacycline 300 mg every 24 hours or oral linezolid 600 mg every 12 hours was allowed after 3 days Total treatment: 7-14 days	Demographics: Age (mean): 47 yrs Male: 64% Infection type: Wound infection: 32% Cellulitis or erysipelas: 39% Major abscess: 28% Key Inclusion Criteria: - 18 years and older - qualifying skin infection, cellulitis, or erysipelas or major abscess - contiguous surface area of at least 75 cm^2 - evidence of erythema, edema, or induration Key Exclusion Criteria: - use of 1 or more potentially effective systemic antibacterial treatment or topical antibiotic within 72 hours of first dose	mITT: 1. 316 2. 311 PP: 1. 269 2. 260 Attrition: 1. 15% 2. 16%	Early Clinical Response (mITT population)‡: O: 268 (84.8%) L: 266 (85.5%) MD -0.7% (95% CI, -6.3 to 4.9) *Noninferior to linezolid* Early Clinical Response (per-protocol population/post-hoc analysis)‡: 14 days after last dose): O: 276 (92.6%) L: 278 (94.6%) MD -1.9% (95% CI, -6.1 to 2.1) Secondary Endpoints: Clinical response at post-treatment evaluation (7 to 14 days after last dose): O:272 (87.1%) L: 260 (83.6%) MD 2.5% (95% CI, -3.2 to 8.2)	NA for all	Discontinuations due to adverse events: O: 6 (1.9%) L: 7 (2.2%) Serious Adverse Events: O: 12 (3.7%) L: 8 (2.5%) Death: O: 1 (0.3%) L: 2 (0.6%) Nausea: O: 40 (12.4%) L: 32 (9.9%) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized in a 1:1 ratio via an interactive voice response/interactive web response system. Performance Bias: (low) double-blind design and trial personal were blinded to treatment assignment. Detection Bias: (high) data analyses and interpretation done by manufacturer. Attrition Bias: (high) Over 10% attrition in both groups. Analysis was done on mITT population. Reporting Bias: (low) Outcomes reported as prespecified. Other Bias: (high) Industry funded. **Applicability**: Patient: In patients with median IV treatment of 4.4 days in both groups and an average of 5.5 days of oral therapy (88% of patients transitioned to oral therapy) with ABSSSI. Intervention: Omadacycline dose was appropriate. Comparator: Linezolid approved for uncomplicated skin and skin structure infections but not recommended first-line in most cases. Outcomes: Clinical response to therapy is an appropriate outcome.

		- only gram-negative pathogens identified (mITT population) - infections thought to require more than 14 days of treatment - chronic (> 3 months) skin lesions, ulcers or wounds - clinically significant liver or renal insufficiency - immunocompromised patients						Setting: Multi-center study in 86 sites in Europe, North America, South America, the Middle East, Africa and Asia.
Abbreviations: ABSSSI = acute bacterial skin or skin structure infection; CABP = community acquired bacterial pneumonia; COPD = chronic obstructive pulmonary disease; DB = double-blind; IV = intravenous; MD = mean difference; mITT = modified intent-to-treat analysis; NI = noninferiority; PSI = pneumonia severity index; PC = placebo-controlled; PG = parallel-group, RCT = randomized controlled trial Key: † early clinical response defined as survival with improvement in at least two of four symptoms (cough, sputum production, pleuritic chest pain and dyspnea) assessed 72 – 120 hours after the first dose; ‡ early clinical response defined as survival with a reduction in lesion size of at least 20% without rescue antibacterial therapy at 48 to 72 hours after first dose of trial drug								

NEW DRUG EVALUATION: Sarecycline

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Sarecycline is a narrow spectrum tetracycline antibiotic that is FDA approved for inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients that are 9 and older.[11] Sarecycline has efficacy against *Propionibacterium Acnes*, including efficacy against erythromycin resistant isolates. Efficacy for the use of sarecycline for the treatment of infections or use beyond 12 weeks has not been evaluated; however, an open-label extension study lasting 40 weeks has been performed. Sarecycline was studied in two, 12-week, double-blind, placebo-controlled trials in a total of 2002 patients ages 9 to 45 years with moderate to severe acne vulgaris (mean Investigator's Global Assessment [IGA] score of 3)(**Table 8**). The IGA score is a non-validated assessment used in clinical trials to evaluate the signs associated with atopic dermatitis (e.g., erythema, lichenification, edema, exudation) based on a six-point scale from clear to severe.[22] The FDA considers a change of 2 grades to be indicative of a success in the treatment of acne.[23] Sarecycline 60 mg, 100 mg, or 150 mg capsules were dosed based on weight with ranges of 1.1 to 1.8 mg/kg once daily.[24] In both trials the co-primary endpoints were: percent of patients achieving IGA success (defined as a score of clear (0) or almost clear (1) and a 2-point decrease from baseline on IGA score at week 12 and absolute reduction from baseline in inflammatory lesions count at week 12) evaluated in the ITT population. The sarecycline trials evaluated inflammatory lesions and noninflammatory lesions; however, noninflammatory lesions were a prespecified secondary endpoint in the second trial only. The Skindex-16 patient reported questionnaire was used to measure patient's quality of life and evaluated patients' symptoms, emotions, and functioning. Scores ranged from 0 (never bothered) to 100 (always bothered).[24] No minimal clinically important change in the Skindex-16 has been described.

In both studies, sarecycline was more effective than placebo for both co-primary endpoints. In the first study, 21.9% of patients in the sarecycline group achieved an IGA score of 0 or 1 compared to 10.5% in the placebo group (ARR 11.4%/NNT 9; p<0.001).[24] The mean absolute reduction in inflammatory lesion count was higher with sarecycline compared to placebo, 15.3 versus 10.2, respectively (P<0.001).[17] Results for the second study were similar with 22.6% of patients in sarecycline group achieving an IGA score of 0 or 1 compared to 15.3% in the placebo group (ARR 7.3%/NNT 14; p=0.004).[17] The absolute change in the number of inflammatory lesions was higher for sarecycline compared to placebo, 15.5 versus 11.1 (p<0.001).[24]

Limitations to this study include a high or unclear risk of bias for selection, detection, reporting and attrition domains. The quality of this study was graded as low quality.

Clinical Safety:
A similar amount of patients experienced adverse events with sarecycline and placebo, 27.7% and 29.2%.[24] The most common adverse event associated with sarecycline is nausea.[11] Like other tetracycline antibiotics sarecycline should not be used in young children and in pregnant women in the second in third trimester. Sarecycline can cause photosensitivity and should be discontinued if signs of *C. diff* or intracranial hypertension.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Number of inflammatory lesions
2) Acne severity
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
2) IGA response and inflammatory lesions

Table 7. Pharmacology and Pharmacokinetic Properties of Sarecycline[11]

Parameter	
Mechanism of Action	Tetracycline antibiotic with unknown mechanism of action against acne
Oral Bioavailability	Not described
Distribution and Protein Binding	91.4 – 97.0 Liter 62.5-74.7% protein bound
Elimination	44.1% urine and 77.5% to 42.6% feces
Half-Life	21-22 hours
Metabolism	<15% from human liver microsomes

Table 8. Comparative Evidence Table for Sarecycline.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Moore, et al[7] Phase 3, DB, RCT, PC, PG (SC 1401)	1. Sarecycline 1.5 mg/kg/day dosed once daily (S) 2. Placebo tablets (P) 12 weeks	Demographics: Age (mean): 20 yrs Male: 45% IGA score of 3: 86% IGA score of 4: 14% Key Inclusion Criteria: - IGA score equal to or greater than 3 - 20-50 inflammatory lesions - 100 or less non-inflammatory lesions - 2 or less nodules Key Exclusion Criteria: - other dermatological condition or facial hair - chronic illness interfering with study evaluation - allergy or resistance to tetracycline antibiotics - drug-induced acne - other medications that could impact acne 12 weeks prior to initiation	ITT: 1. 483 2. 485 PP: 1. 463 2. 403 Attrition: 1. 4% 2. 16%	Co-primary Endpoints: IGA Success*: S: 106 (21.9%) P: 51 (10.5%) P<0.0001 CI not reported Mean absolute change in inflammatory lesions: S: 250 (-51.8%) P: 170 (-35%) P<0.0001 Secondary Endpoints: Skindex-16 total score†: MD -3.5 (95% CI, -6.0 to -1.1) P <0.05	11%/9 NA NA	Nausea: S: 22 (4.6%) P: 12 (2.5%) Nasopharyngitis S: 15 (3.1%) P: 8 (1.7%) Headache: S: 13 (2.7%) P: 13 (2.7%) Discontinuations due to adverse events: S: 3 (0.6%) P: 7 (1.4%) Serious Adverse Events: S: 4 (0.6) P: 5 (1.0) p-value not reported for all	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization procedures not described. Balanced baseline characteristics Performance Bias: (low) Matching tablets to prevent unblinding. Double-blind design but details not provided Detection Bias: (unclear) Outcome assessment not described. Attrition Bias: (high) Twelve percent difference in discontinuation rates between groups could bias results. Analysis was done on the ITT population with a multi-imputation approach for missing data Reporting Bias: (high) Outcomes reported as prespecified but lacked confidence intervals Other Bias: (high) Industry funded **Applicability**: Patient: In patients with inflammatory moderate to severe acne Intervention: Intervention appropriate Comparator: Active treatment comparison would helpful to determine comparative efficacy Outcomes: IGA scores and number of acne lesions are common outcomes used in studies evaluating efficacy of acne treatment Setting: Multi-center study in over 100 sites within the United States
2. Moore, et al[7] Phase 3, DB, RCT, PC, PG (SC 1402)	1. Sarecycline 1.5 mg/kg/day dosed orally once daily (S) 2. Placebo tablets (P) 12 weeks	Demographics: Age (mean): 20 years Male: 41% IGA score of 3: 85% IGA score of 4: 15% Key Inclusion Criteria: - IGA score equal to or greater than 3	ITT: 1. 519 2. 515 PP: 1. 427 2. 442 Attrition: 1. 17%	Co-primary Endpoints: IGA Success*: S: 117 (22.6%) P: 79 (15.3%) P=0.004 CI not reported Mean absolute change in inflammatory lesions: S: 259 (-49.9%)	7%/14	Nausea: S: 10 (1.9%) P: 5 (1.0%) Nasopharyngitis S: 13 (2.5%) P: 15 (2.9%) Headache: S: 15 (2.9%)	NA for all	**Risk of Bias (low/high/unclear)**: See above

		- 20-50 inflammatory lesions - 100 or less non-inflammatory lesions - 2 or less nodules <u>Key Exclusion Criteria</u>: - other dermatological condition or facial hair - chronic illness interfering with study evaluation - allergy or resistance to tetracycline antibiotics - drug-induced acne - other medications that could impact acne 12 weeks prior to initiation	2. 14%	P: 182 (-35.4%) P<0.0001 <u>Secondary Endpoints</u>: Absolute percent change of noninflammatory lesions (in patients with 20 or more inflammatory lesions at baseline): S: 84 (16.2%) P: 69 (13.4%) P<0.01 Skindex-16 total score†: MD -5.9 (95% CI, -8.1 to -3.6) P <0.05	NA NA NA	P: 25 (4.9%) <u>Discontinuations due to adverse events:</u> S: 11 (2.1%) P: 6 (1.2%) <u>Serious Adverse Events</u>: S: 4 (0.8) P: 1 (0.2) p-value not reported for all		
Key: * IGA – 2 or more grade improvement and score 0 (clear) or 1 (almost clear), † Individual group results not reported Abbreviations: DB = double-blind; IGA = Investigator's Global Assessment; MD = mean difference; NA = not applicable: PC = placebo-controlled; PG = parallel-group, RCT = randomized controlled trial								

References:

1. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing. December 5, 2018. Available at: nice.org.uk/guidance/ng114. Accessed December 13, 2018.
2. National Institute for Health and Care Excellence. Sinusitits (acute): antimicrobial prescribing. October 27, 2017. Availabe at: nice.org.uk/guidance/ng79. Accessed December 12, 2018.
3. National Institute for Health and Care Excellence. Lyme Disease. NICE Guideline. 4/11/2018. Available at: https://www.nice.org.uk/guidance/ng95/resources/lyme-disease-pdf-1837756839877. Accessed 12/10/18.
4. Savaris RF, Fuhrich DG, Duarte RV, Franik S, Ross J. Antibiotic therapy for pelvic inflammatory disease (Review). *Cochrane Database of Systematic Reviews*. Issue 4. Art. No.: CD010285.DOI: 10.1002/14651858.CD010285.pub2.
5. Stets R, Popescu M, Gonong J, et al. Omadacycline for community-aquired bacterial penumonia. *NEJM*.2019:380;517-27.
6. O'Riordan W, Green S, Overcash S, et al. Omadacycline for acute bacterial skin and skin-structure infections. *NEJM*.2019;380:528-38.
7. Moore A, Green L, Bruce S, 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 of Drugs in Dermatology*. 2018;17(9):987-996.
8. May B. Tetracyclines. Up To Date. November 29, 2018. Available at: www.uptodate.com. Accessed 12/27/18.
9. Stevens D, Bisno A, Chambers H, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clinical Infectious Disease*; 2014:59(2):e10-52.

10. Nuzyra Prescribing Information. Paratek Pharmaceuticals, Inc. Boston, MA. 2018.
11. Seysara Prescribing Information. Allergan Pharmaceuticals, Inc. Madison, NJ. 2018.
12. Malhotra K, Chang JJ, Khunger A, et al. Minocycline for acute stroke treatment: a systematic review and meta-analysis of randomized clinical trials. [Review]. *Journal of Neurology*. 2018;265(8):1871-1879. doi:10.1007/s00415-018-8935-3
13. Canadian Agency for Drugs and Technologies in Health. Mangement and treatment of cervicitis: a review of clinical effectiveness and guidelines. Rapid Response Report. Septermber 2017. Available at: https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0926%20Cervicitis%20Revised%20Final.pdf. Accessed 12/20/18.
14. Ayeleke RO, Mourad S, Marjoribanks J, Calis KA, Jordan V. Antibiotic prophylaxis for elective hysterectomy. [Review]. *Cochrane Database of Systematic Reviews*. 2017;1:CD004637. doi:10.1002/14651858.CD004637.pub2
15. Rosenblat JD, McIntyre RS. Efficacy and tolerability of minocycline for depression: A systematic review and meta-analysis of clinical trials. [Review]. *Journal of Affective Disorders*. 2018;1:219-225. doi:10.1016/j.jad.2017.10.042
16. Minolira Package Insert. Promius Pharma, LLC. Princeton, NJ. 2017.
17. Food and Drug Administration. Xyrosa new drug approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209259Orig1s000TAltr.pdf. Accessed 1/5/18.
18. Lymepack Prescribing Information. Chartwell Pharmaceuticals, LLC., Congers NY. 2018.
19. Food and Drug Administration. Drug Safety Label Changes: doxycycline. November 15, 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1376. Accessed 12/20/18.
20. Center for Drug Research and Evaluation. Omadacycline Multi-disciplinary Review. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209816Orig1s000,209817Orig1s000MultidisciplineR.pdf. Accessed January 3, 2018.
21. Paratek Pharmaceuticals. Nuzyra (omadacycline) AMCP dossier. January 2019.
22. Chopra R, Silverberg J. Assessing the severity of atopic dermatitis in clinical trials and practice. *Clinics in Dermatology*. 2018;36:606-615.
23. Food and Drug Administration. Acne vulgaris:establishing effectiveness of drugs intended for treatment guidance for industry. FDA Center for Drug Evaluation and Research. May 2018. Available at: https://www.fda.gov/downloads/Drugs/Guidances/UCM071292.pdf. Accessed February 19, 2019.
24. Food and Drug Administration. Sarecycline Multi-Dicipline Review. Center for Drug Evaluation and Research. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209521Orig1s000MultidisciplineR.pdf. Accessed January 7, 2019.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET	Y
doxycycline hyclate	DOXYCYCLINE HYCLATE	CAPSULE	Y
doxycycline hyclate	ED DOXY-CAPS	CAPSULE	Y
doxycycline hyclate	MORGIDOX	CAPSULE	Y
doxycycline hyclate	VIBRAMYCIN	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	CAPSULE	Y
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	SUSP RECON	Y
doxycycline monohydrate	VIBRAMYCIN	SUSP RECON	Y

tetracycline HCl	ALA-TET	CAPSULE	Y
tetracycline HCl	TETRACYCLINE HCL	CAPSULE	Y
doxycycline calcium	VIBRAMYCIN	SYRUP	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET	N
doxycycline hyclate	LYMEPAK	TABLET	N
doxycycline hyclate	DORYX	TABLET DR	N
doxycycline hyclate	DORYX MPC	TABLET DR	N
doxycycline hyclate	DOXYCYCLINE HYCLATE	TABLET DR	N
doxycycline monohydrate	DOXYCYCLINE IR-DR	CAP IR DR	N
doxycycline monohydrate	ORACEA	CAP IR DR	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	CAPSULE	N
doxycycline monohydrate	ADOXA	TABLET	N
doxycycline monohydrate	ADOXA PAK	TABLET	N
doxycycline monohydrate	DOXYCYCLINE MONOHYDRATE	TABLET	N
minocycline HCl	XIMINO	CAP ER 24H	N
minocycline HCl	DYNACIN	CAPSULE	N
minocycline HCl	MINOCIN	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL	CAPSULE	N
minocycline HCl	MINOCYCLINE HCL ER	TAB ER 24H	N
minocycline HCl	SOLODYN	TAB ER 24H	N
minocycline HCl	MINOCYCLINE HCL	TABLET	N
demeclocycline HCl	DEMECLOCYCLINE HCL	TABLET	N
omadacycline	NUZYRA	TABLET/IV	N
sarecycline	SEYSARA	TABLET	N

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to November Week 5 2018
Search Strategy:

#	Searches	Results
1	doxyclycline.mp.	4
2	tetracycline.mp.	37597
3	minocycline.mp. or MINOCYCLINE/	7691
4	demeclocycline.mp. or DEMECLOCYCLINE/	988
5	omadacycline.mp.	29
6	1 or 2 or 3 or 4 or 5	44352
7	limit 6 to (structured abstracts and english language and humans and yr="2017 -Current")	319
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	23

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUZYRA™ safely and effectively. See full prescribing information for NUZYRA.

NUZYRA (omadacycline) for injection, for intravenous use
NUZYRA (omadacycline) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
NUZYRA is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms (1):

- Community-acquired bacterial pneumonia (CABP) (1.1)
- Acute bacterial skin and skin structure infections (ABSSSI) (1.2)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.3)

----------DOSAGE AND ADMINISTRATION----------
- Dosage of NUZYRA in CABP and ABSSSI Adult Patients (2.2, 2.3):

Infection	Loading Doses	Maintenance Dose
CABP	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.2)	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.2)
ABSSSI	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.3) OR	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.3)
ABSSSI (NUZYRA tablets only)	Day 1 and Day 2: 450 mg orally once daily (2.3)	300 mg orally once daily (2.3)

- CABP and ABSSSI: Treatment duration is 7 to 14 days. (2.2, 2.3)
- Fast for at least 4 hours and then take NUZYRA tablets with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours. (2.1)
- See full prescribing information for the preparation of NUZYRA IV and other administration instructions. (2.1, 2.5).

----------DOSAGE FORMS AND STRENGTHS----------
- For Injection: 100 mg of omadacycline (equivalent to 131 mg omadacycline tosylate) as a lyophilized powder in a single dose vial for reconstitution and further dilution before intravenous infusion (3.1)
- Tablets: 150 mg omadacycline (equivalent to 196 mg omadacycline tosylate) (3.2)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to omadacycline, tetracycline-class antibacterial drugs or any of the excipients in NUZYRA (4)

----------WARNINGS AND PRECAUTIONS----------
- Mortality Imbalance in Patients with CABP: In the CABP trial, mortality rate of 2% was observed in NUZYRA-treated patients compared to 1% in moxifloxacin-treated patients. The cause of the mortality imbalance has not been established. Closely monitor clinical response to therapy in CABP patients, particularly in those at higher risk for mortality. (5.1, 6.1)
- Tooth Discoloration and Enamel Hypoplasia: The use of NUZYRA during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown) and enamel hypoplasia. (5.2, 8.1, 8.4)
- Inhibition of Bone Growth: The use of NUZYRA 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. (5.3, 8.1, 8.4).
- *Clostridium difficile*-associated diarrhea: Evaluate if diarrhea occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Paratek Pharmaceuticals, Inc. at 1-833-727-2835 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage while taking NUZYRA. (7.1)
- Absorption of tetracyclines, including NUZYRA is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron containing preparations. (2.1, 7.2)

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Breastfeeding is not recommended during treatment with NUZYRA. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SEYSARA™ safely and effectively. See full prescribing information for SEYSARA™.

SEYSARA™ (sarecycline) tablets for oral use.
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
SEYSARA™ is a tetracycline-class drug indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older. (*1*)

Limitations of Use
Efficacy of SEYSARA beyond 12 weeks and safety beyond 12 months have not been established. SEYSARA has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SEYSARA should be used only as indicated *[see Warnings and Precautions (5.6)]*.

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage of SEYSARA is once daily with or without food:
- 60 mg for patients who weigh 33-54 kg,
- 100 mg for patients who weigh 55-84 kg,
- 150 mg for patients who weigh 85-136 kg. (*2*)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 60 mg, 100 mg, 150 mg (*3*)

----------CONTRAINDICATIONS----------
SEYSARA is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (*4*)

----------WARNINGS AND PRECAUTIONS----------
- The use of SEYSARA during tooth development (second and third trimesters of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (*5.1*)
- If Clostridium difficile Associated Diarrhea (antibiotic associated colitis) occurs, discontinue SEYSARA. (*5.2*)
- Central nervous system side effects, including light-headedness, dizziness or vertigo, have been reported with tetracycline use. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery. These symptoms may disappear during therapy and may disappear when the drug is discontinued. (*5.3*)
- SEYSARA may cause intracranial hypertension. Discontinue SEYSARA if symptoms occur. (*5.4*)
- Photosensitivity can occur with SEYSARA. Patients should minimize or avoid exposure to natural or artificial sunlight. (*5.5*)

----------ADVERSE REACTIONS----------
Most common adverse reaction (incidence ≥ 1%) is nausea. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Oral retinoids: avoid coadministration. (*5.4, 7.1*)
- Antacids and iron preparations: separate dosing of SEYSARA. (*7.1*)
- Penicillin: avoid coadministration. (*7.2*)
- Anticoagulants: decrease anticoagulant dosage as appropriate. (*7.2*)
- P-glycoprotein substrates: monitor for toxicities of drugs that may require dosage reduction. (*7.2*)

----------USE IN SPECIFIC POPULATIONS----------
- Sarecycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. (*5.1, 8.1*)
- The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of teeth. (*5.1, 8.4*)
- Lactation: Breastfeeding is not recommended. (*8.2*)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2018

Appendix 4: Key Inclusion Criteria

Population	Children and adults with an indication for tetracycline antibiotics
Intervention	Tetracycline therapy
Comparator	Placebo or active treatment
Outcomes	Clinical cure rate, reinfection, lesion reduction
Timing	Not applicable
Setting	Outpatient therapy