09-J3000-72

Original Effective Date: 09/15/20

Reviewed: 12/13/23

Revised: 01/15/24

Subject: Omadacycline (Nuzyra®) Tablets

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DESCRIPTION:

Omadacycline (Nuzyra) is an oral and intravenous (IV) aminomethylcycline antibiotic within the tetracycline class that was approved by the US Food and Drug Administration (FDA) in October 2018 for the treatment of adult patient with community-acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms. Omadacycline has shown activity against organisms expressing tetracycline-specific resistance mechanisms, including efflux and ribosomal protection. The current guidelines from the Infectious Diseases Society of America (IDSA) for CAP (2019) and ABSSSI (2014) do not include omadacycline as a recommendation. The CAP guidelines mention that omadacycline needs further validation in the outpatient setting. For inpatient settings, due to only a single published report and the safety information being less well established, the committee decided to not list omadacycline as an alternative to the currently recommended treatment options.

The safety and efficacy of omadacycline leading to FDA approval was established in three randomized studies (two for ABSSSI and one for CAP). In the randomized study of adults with CAP (n=774, NCT02531438), clinical success rates with omadacycline were similar to those with moxifloxacin. Omadacycline was administered 100 mg IV every 12 hours for two doses on Day 1, followed by 100 mg IV daily, or 300-mg orally, daily. Moxifloxacin 400 mg was administered IV or orally daily. Total treatment duration was 7 to 14 days. All enrolled patients were expected to require a minimum of at least 3 days of IV treatment. Early success rates (72 to 120 hours after first dose), defined as survival with improvement in at least 2 symptoms (cough, chest pain, sputum production, dyspnea) without deterioration in the intent to treat population (ITT), which consisted of all randomized patients, were 81.1% with omadacycline and 82.7% with moxifloxacin. Post-treatment success rates (5 to 10 days after last dose), defined as survival and improvement of symptoms with no further antibiotic therapy necessary in the ITT population, were 87.6% with omadacycline and 85.1% with moxifloxacin. Post-treatment success rates based on baseline organism were similar between treatment groups.

In the two randomized studies of adult with ABSSSI (cellulitis, major abscess, or wound infection) and at least 1 gram-positive causative organism (n=1,390, NCT02378480 and 02877927), success rates with omadacycline were similar to those achieved with linezolid. Mean wound surface area at baseline ranged from 399 to 498 cm^2. Omadacycline was administered 100 mg IV every 12 hours for two doses on Day 1, followed by 100 mg IV daily, or 300-mg orally, daily (study 1) or 450 mg oral once a day on Days 1 and 2, followed by 300-mg orally once a day (study 2). Linezolid was administered 600 mg IV every 12 hours, with the option to switch to 600 mg orally every 12 hours (study 1) or 600 mg orally every 12 hours (study 2). Total treatment duration was 7 to 14 days. Early success rates (48 to 72 hours after first dose), defined as at least a 20% decrease in lesion size in the modified ITT population, defined as all randomized subjects without a sole Gram-negative causative pathogen at screening, were 84.8% with omadacycline and 85.5% with linezolid in study 1 and 87.3% and 82.2%, respectively, in study 2. Post-treatment success rates (7 to 14 days after last dose), defined as survival with no alternative antibiotic therapy, no unplanned major surgery, and no further antibiotic therapy deemed necessary in the mITT population, were 86.1% with omadacycline and 83.6% with linezolid in study 1. Success rates in study 2 were 83.9% and 80.5%, respectively. Post-treatment success rates based on baseline organism were similar between treatment groups.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Use of omadacycline (Nuzyra) tablets **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", and "3"):

1. **ANY** of the following ("a", "b", "c", or "d"):
    a. Member started treatment with omadacycline in an acute care hospital, and now requires continued outpatient therapy with the oral tablets upon hospital discharge
    b. Outpatient treatment of community-acquired bacterial pneumonia (CABP), and **EITHER** of the following ("i" or "ii"):
        i. Inadequate response or intolerance to at least **ONE** formulary antibiotic clinically appropriate for the treatment of CABP, unless **ALL** appropriate formulary antibiotics are contraindicated – the medications previously tried, and the specific contraindication(s) and/or intolerance(s), if applicable, must be provided
        ii. A culture and sensitivity (C&S) report shows resistance or lack of susceptibility of the isolated pathogen to **ALL** formulary antibiotics FDA-approved for CABP
    c. Outpatient treatment of acute bacterial skin and skin structure infections (ABSSSI), and **EITHER** of the following ("i" or "ii"):
        i. Inadequate response or intolerance to at least **ONE** formulary antibiotic clinically appropriate for the treatment of ABSSSI, unless **ALL** appropriate formulary antibiotics are

contraindicated – the medications previously tried, and the specific contraindication(s) and/or intolerance(s), if applicable, must be provided

ii. A C&S report shows resistance or lack of susceptibility of the isolated pathogen to **ALL** formulary antibiotics FDA-approved for ABSSSI

d. Outpatient treatment of a non-CABP or non-ABSSSI infection, and **BOTH** of the following ("i" and "ii"):

i. Treatment with omadacycline is recommended by the Centers for Disease Control and Prevention (CDC) or in an Infectious Diseases Society of America (IDSA) guideline – the applicable CDC publication or IDSA guideline must be submitted

ii. Omadacycline is being used in accordance with the specific recommendations in the applicable CDC publication or IDSA guideline (for example, multidrug resistant infections or allergy to alternative antibiotics) – if applicable, the medications previously tried, contraindication(s), and/or intolerance(s) must be provided

2. The member has **NOT** previously received a separate treatment course of omadacycline in the past 6 months

3. The dosage of omadacycline does not exceed the following based on the indication ("a", "b", or "c"):

a. CABP

i. 300 mg (two 150 mg tablets) twice on day 1

ii. 300 mg (two 150 mg tablets) once a day not to exceed 14 total days of treatment (i.e., IV and oral treatment days combination)

b. ABSSSI:

i. 450 mg (three 150 mg tablet) once a day on days 1 and 2

ii. 300 mg (two 150 mg tablets) once a day not to exceed 14 total days of treatment (i.e., IV and oral treatment days combination)

c. Other CDC- or IDSA-recommended indication – the dose and duration does not exceed the recommendation in the applicable CDC publication or IDSA guideline.

Approval duration:

- CABP and ABSSSI - 1 month [to allow up to a 14-day total course of treatment (up to thirty 150-mg tablets)]
- Other CDC- or IDSA-recommended indication – the CDC- or IDSA-recommended treatment duration, up to 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: Streptococcus pneumoniae, Staphylococcus aureus (methicillin-susceptible isolates), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydophila pneumoniae.
    - Loading dose - 200 mg by IV infusion over 60 minutes on day 1; 100 mg by IV infusion over 30 minutes, twice on day 1; **OR** 300 mg orally twice on day 1
    - Maintenance Dose - 100 mg by IV infusion over 30 minutes once daily, or 300 mg orally once daily
    - Treatment duration - 7 to 14 days
- Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by the following susceptible microorganisms: Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), Enterococcus faecalis, Enterobacter cloacae, and Klebsiella pneumoniae.
    - Loading dose - 200 mg by IV infusion over 60 minutes on day 1; 100 mg by IV infusion over 30 minutes, twice on day 1; OR 450 mg orally once a day on day 1 and day 2
    - Maintenance Dose - 100 mg by IV infusion over 30 minutes once daily, or 300 mg orally once daily
    - Treatment duration - 7 to 14 days
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of omadacycline and other antibacterial drugs, omadacycline should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy
- For the oral tablet, fast for at least 4 hours and then take 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.

Dose Adjustments

- No dosage adjustment is warranted in patients with renal or hepatic impairment

Drug Availability

- Injection - 100 mg sterile lyophilized powder in a single-dose colorless glass vial packaged in cartons of 10
- Tablets - 150 mg tablets in blister package of 6 or blister package of 30 (5 blister cards of 6 tablets each)

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Known hypersensitivity to omadacycline, tetracycline-class antibacterial drugs or any of the excipients in Nuzyra

Precautions/Warnings

- **Mortality Imbalance in Patients with Community-Acquired Bacterial Pneumonia**: Mortality imbalance was observed in the CABP clinical trial with eight deaths (2%) occurring in patients treated with omadacycline compared to four deaths (1%) in patients treated with moxifloxacin. The cause of the mortality imbalance has not been established. All deaths, in both treatment arms, occurred in patients > 65 years of age; most patients had multiple comorbidities. The causes of death varied and included worsening and/or complications of infection and underlying conditions. Closely monitor clinical response to therapy in CABP patients, particularly in those at higher risk for mortality.
- **Tooth Discoloration and Enamel Hypoplasia**: **T**he use of omadacycline during tooth development (last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the tetracycline class drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported with tetracycline class drugs. Advise the patient of the potential risk to the fetus if omadacycline is used during the second or third trimester of pregnancy.
- **Inhibition of Bone Gr**owth: The use of omadacycline during the second and third trimester of pregnancy, infancy and childhood up to the age of 8 years may cause reversible inhibition of bone growth. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. Advise the patient of the potential risk to the fetus if omadacycline is used during the second or third trimester of pregnancy.
- **Hypersensitivity Reactions**: Hypersensitivity reactions have been reported with omadacycline. Life-threatening hypersensitivity (anaphylactic) reactions have been reported with other tetracycline-class antibacterial drugs. Omadacycline is structurally similar to other tetracycline-class antibacterial drugs and is contraindicated in patients with known hypersensitivity to tetracycline-class antibacterial drugs. Discontinue omadacycline if an allergic reaction occurs.
- **Clostridium difficile-Associated Diarrhea**: Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- **Tetracycline Class Effects**: Omadacycline is structurally similar to tetracycline-class of antibacterial drugs and may have similar adverse reactions. Adverse reactions including photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased BUN, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver function tests, have been reported for other tetracycline-class antibacterial drugs, and may occur with omadacycline. Discontinue omadacycline if any of these adverse reactions are suspected.
- **Development of Drug-Resistant Bacteria**: Prescribing omadacycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Hemophilus influenzae
J15.0 – J15.9	Bacterial pneumonia, not elsewhere classified
L00 – L08.9	Infections of the skin and subcutaneous tissue

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/13/23.

GUIDELINE UPDATE INFORMATION:

09/15/20	New Medical Coverage Guideline.
07/15/21	Revision to guidelines consisting of updating the position statement, dosage/administration, and references.
01/15/22	Review and revision to guidelines consisting of updating the references.

01/15/23	Review and revision to guidelines consisting of updating the position statement and references. Clarified requirement when omadacycline is started in an acute care hospital and added an allowance for use when recommended by a CDC publication.
09/15/23	Revision to guidelines consisting of updating the position statement to remove the requirement of a culture and sensitivity (C&S) report and change the prior antibiotic trial requirement from at least two formulary antibiotics to at least one clinically appropriate formulary antibiotic.
01/15/24	Review and revision to guidelines consisting of updating the references.