Brand Name: Nuzyra

Generic Name: omadacycline

Manufacturer[1]**:** Paratek Pharmaceuticals, Inc.

Drug Class[1,2,3,4,5]**:** Antibiotic, Tetracycline Derivative

Uses:

Labeled Uses[1,2,3,4,5]: Community-acquired bacterial pneumonia (CABP); Infection of skin and/or subcutaneous tissue
Unlabeled Uses[2]: None

Mechanism of Action[2,3,4,5]:

Omadacycline is an aminomethylcycline antibacterial within the tetracycline class of antibacterial drugs. It blocks protein synthesis by binding to the 30S ribosomal subunit and preventing the incorporation of amino acid residues into elongating peptide chains. In general, omadacycline is bacteriostatic against gram-positive bacteria, but has demonstrated gram-negative activity against certain strains, such as *Haemophilus influenzae.*

Pharmacokinetics[1,2,3,4,5]**:**

Absorption:

T_{max}	~0.5 hours IV; 2.5 hours PO
V_d	190L IV; 794L PO
$t_{½}$	~16 hours IV; 15.5-16.83 PO
Clearance	2.4-3.3 L/hr (renal)
Protein binding	20% (extent to albumin not reported)
Bioavailability	34.5%

Metabolism: In vitro studies using human liver microsomes and hepatocytes demonstrated that omadacycline does not undergo metabolism. It is a P-glycoprotein (P-gp) substrate. Administration of oral verapamil (P-gp inhibitor) 2 hours prior to a single 300 mg dose of omadacycline increased omadacycline AUC by approximately 25% and Cmax by approximately 9%.

Elimination: Drug elimination depends on route of administration. After IV administration, 27% of the dose is eliminated in the urine as unchanged drug. After oral administration, 77.5% to 84% of the dose is recovered in feces while excretion in the urine accounts for approximately 14.4% of the dose.

Efficacy:

Stets R, Popescu M, Gonong JR, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. *N Engl J Med.* 2019 Feb 7;380(6):517-527[6].

Study Design: Phase 3, multicenter, double-blind, double-dummy, randomized, noninferiority trial

Description of Study:

Methods: Adults with CABP (Pneumonia Severity Index risk class II, III, or IV) were randomized to receive omadacycline 100 mg IV every 12 hours for two doses, then 100 mg IV every 24 hours, or moxifloxacin 400 mg IV every 24 hours. A transition to oral omadacycline 300 mg every 24 hours or moxifloxacin 400 mg every 24 hours, respectively, was allowed after 3 days. The total treatment duration was 7-14 days. The primary end point was early clinical response at 72-120 hours, without receipt of rescue antibacterial therapy. A secondary end point was investigator-assessed clinical response at a post-treatment evaluation 5-10 days after the last dose. A noninferiority margin of 10 percentage points was used. Safety variables that were assessed included adverse events, clinical laboratory evaluations, vital signs, and electrocardiographic findings. In addition, microbiological response for each baseline pathogen was determined at the end of treatment at the post-treatment evaluation visits.

Outcome Results: The intention-to-treat population included 386 patients in the omadacycline group and 388 patients in the moxifloxacin group. Omadacycline (81.1%) was noninferior to moxifloxacin (82.7%) for early clinical response (difference -1.6 percentage points; 95% CI -7.1-3.8). The rates of investigator-assessed clinical response at the post-treatment evaluation were 87.6% and 85.1% for omadacycline and moxifloxacin, respectively (difference 2.5 percentage points; 95% CI -2.4-7.4). Adverse events were reported in 41.1% of patients in the omadacycline group and 48.5% of patients in the moxifloxacin group. The most frequent adverse events were gastrointestinal (10.2% and 18.0%, respectively). The largest difference was for diarrhea (1.0% and 8.0%, respectively). Twelve deaths (8 in the omadacycline group and 4 in the moxifloxacin group) occurred during the trial.

Limitations: This study was sponsored by Paratek Pharmaceuticals, the manufacturer of omadacycline. Seven authors report being employed by and holding stock in Paratek Pharmaceuticals, introducing a potential conflict of interest. There are a few limitations that make it hard to extrapolate to real clinical practice: most patients were from Eastern Europe, the moxifloxacin group had slightly older patients as well as more patients with more severe CABP, and the study identified pathogens that cause CABP at baseline in 49.9% of patients. In practice, pathogens are only identified in ~10% of cases or less.

Conclusion: This study showed that once-daily omadacycline, administered IV with the option of transition to oral administration, was noninferior to moxifloxacin as empirical monotherapy for non-ICU hospitalized adults with CABP. This supports the effectiveness

of using omadacycline as an alternative therapy in CABP. However, more studies need to be conducted in more defined subsets of patients with various causative pathogens for CABP, as well as in varying age groups (geriatric and pediatric populations). Also, comparison studies with other comparator antibiotics, other than moxifloxacin, are needed.

O'Riordan W, Green S, Overcash S, et al. Omadacycline for Acute Bacterial Skin and Skin-Structure Infections. *N Engl J Med.* 2019 Feb 7;380(6):528-538[7].

Study Design: Phase 3, multicenter, double-blind, double-dummy, randomized, noninferiority trial

Description of Study:

Methods: Adults with acute bacterial skin and skin-structure infections were randomly assigned to receive omadacycline 100 mg IV every 12 hours for two doses then 100 mg IV every 24 hours or linezolid 600 mg IV every 12 hours. A transition to oral omadacycline 300 mg every 24 hours or oral linezolid 600 mg every 12 hours was allowed after 3 days. The total treatment duration was 7-14 days. The primary end point was an early clinical response at 48-72 hours. A secondary end point was an investigator-assessed clinical response at the post-treatment evaluation 7-14 days after the last dose. For both end points, the noninferiority margin was 10 percentage points. Safety was assessed on the basis of adverse events, vital signs, electrocardiograms, and laboratory results. In addition, microbiological response for each baseline pathogen was determined at the end of treatment and post-treatment evaluation visits.

Outcome Results: In the modified intention-to-treat population, omadacycline (316 patients) was noninferior to linezolid (311 patients) with respect to early clinical response (rate of response 84.8% and 85.5%, respectively; difference -0.7 percentage points; 95% CI -6.3-4.9). Omadacycline was also noninferior to linezolid with respect to investigator-assessed clinical response at the post-treatment evaluation in the modified intention-to-treat population (rate of response 86.1% and 83.6%, respectively; difference 2.5 percentage points; 95% CI -3.2-8.2) and in the clinical per-protocol population (96.3% and 93.5%, respectively; difference 2.8 percentage points; 95% CI -1.0-6.9). In both groups, the efficacy of the trial drug was similar for methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* infections. Adverse events were reported in 48.3% of patients in the omadacycline group and in 45.7% of patients in the linezolid group. The most frequent adverse events in both groups were gastrointestinal (18.0% and 15.8%, respectively).

Limitations: This study was sponsored by Paratek Pharmaceuticals, the manufacturer of omadacycline. In addition, patients with commonly treated infections acquired in the community (bite wounds and chronic skin infections like diabetic foot ulcers) were excluded, making it harder to extrapolate the results into clinical practice. The study also grouped many types of skin infections with varying causative organisms, leading to differing microbiologic causes and treatment guidelines. In addition, it is unclear what

geographic regions the patients were enrolled from, making it difficult to extrapolate based on varying resistance patterns. Further, the study was underpowered to determine noninferiority within the individual subtypes of infection, making it even more difficult to extrapolate the data.

Conclusion: The results of the study showed that omadacycline was noninferior to linezolid for the treatment of acute bacterial skin and skin-structure infections and had a similar safety profile. This supports the effectiveness of using omadacycline as an alternative therapy in skin and skin-structure infections. However, more studies need to be conducted in more defined subsets of patients with various causative pathogens for skin infections, as well as in varying age groups (geriatric and pediatric populations). Also, comparison studies with other comparator antibiotics, other than linezolid, are needed.

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 Nov;56(11):5650-4[8].

Study Design: Phase 2, multicenter, investigator-blind, randomized trial

Description of Study:

Methods: Patients with complicated skin and skin structure infections (cSSSI) were randomized to omadacycline 100 mg IV once daily with an option to transition to 200 mg orally or linezolid 600 mg IV twice daily with an option to transition to 600 mg twice daily. The primary hypothesis tested was the safety and tolerability of omadacycline compared to linezolid (by assessing adverse events). The secondary hypothesis tested was the rate of successful clinical response at the test of cure evaluation among omadacycline-treated cSSSI patients.

Outcome Results: Adverse events were reported in 41.4% omadacycline-treated patients and in 50.9% linezolid-treated patients. The gastrointestinal tract was most commonly involved, with adverse events reported in 18.9% omadacycline-treated patients and in 18.5% linezolid-treated patients. Rates of successful clinical response in the intention-to-treat (ITT) and clinical evaluable populations favored omadacycline (ITT: 88.3% versus 75.9%; 95% CI: 1.9 to 22.9). For microbiologically evaluable patients with S. aureus infections, the clinical success rates were 97.2% in omadacycline-treated patients 92.7% in linezolid-treated patients.

Limitations: This study was sponsored by Paratek Pharmaceuticals, the manufacturer of omadacycline. This is a big limitation, especially since the authors concluded that omadacycline was well tolerated and effective in treated patients with serious infections of the skin and soft tissues. Another big limitation of the study was the trial design, which limited the study to patients being transitioned from IV to oral therapy during the first 72

hours of therapy. Also, no power was reported, so it is hard to extrapolate the results to clinical practice.

Conclusion: Although the authors concluded that omadacycline is well tolerated and effective in treating serious infections of the skin and soft tissue, I would not extrapolate this to clinical practice. No power or p values were reported. In addition, the confidence intervals reported were very broad in range. More studies are needed in the use of oral omadacycline to determine its safety and tolerability, before comparing it to other comparator antibiotics.

Contraindications[1,2,3,4,5]**:**

Known omadacycline hypersensitivity or tetracyclines hypersensitivity or hypersensitivity to any of the excipients: Discontinue omadacycline therapy if an allergic reaction occurs.

Precautions[1,2,3,4,5]**:**

Death: Increased risk of mortality in patients with CABP, especially in patients >65 years of age and patients with comorbidities; monitoring recommended, especially patients at higher risk for mortality.

Dermatologic: Photosensitivity has been reported with other tetracycline antibiotics; discontinue use if condition occurs.

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

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

Immunologic: Hypersensitivity reactions have been reported and life-threatening hypersensitivity reactions have been reported with other tetracycline antibiotics, discontinue if an allergic reaction occurs; Bacterial resistance to tetracyclines may occur during therapy.

Musculoskeletal: Reversible inhibition of bone growth may occur when used during the second or third trimesters of pregnancy, infancy, and childhood up to the age of 8, reversible upon discontinuation; Decrease in fibula growth has been observed in premature infants given tetracycline, typically reversible upon discontinuation.

Neurologic: Pseudotumor cerebri may occur and has been reported with other tetracycline antibiotics; discontinue if condition occurs.

Photosensitivity: The photosensitizing class effect of tetracycline antibiotics may enhance the photosensitizing effects of other drugs.

Pregnancy: Omadacycline's fetal risk cannot be ruled out. Tetracyclines accumulate in developing teeth and long tubular bones. Permanent discoloration of teeth can occur following in utero exposure and is more likely to occur in the second or third trimesters and following long-term or repeated exposure. Reversible inhibition of bone growth may occur following maternal use of tetracyclines in the second and third trimesters. Due to the potential for adverse pregnancy outcomes, the manufacturer recommends effective contraception for females of reproductive potential during omadacycline therapy.

Lactation: Omadacycline's infant risk cannot be ruled out. It is not known if omadacycline is present in breast milk. As a class, tetracyclines have generally been avoided in breastfeeding females due to concerns that they may cause adverse events in the breastfeeding infant, including tooth discoloration and inhibition of bone growth. Due to the potential for adverse events, the manufacturer does not recommend breastfeeding during therapy or for four days after the last omadacycline dose.

Pediatrics Use: Omadacycline may cause reversible inhibition of bone growth when used during the second or third trimesters of pregnancy, infancy, and childhood ≤8 years. It may cause tooth enamel hypoplasia or permanent tooth discoloration (more common with long-term use, but observed with repeated, short courses) when used during tooth development (last half of pregnancy, infancy, and childhood ≤8 years). Avoid use in children <8 years.

Geriatric Use: Numerically lower clinical success rates at the early clinical response timepoint were observed in CABP patients ≥65 years compared to patients <65 years. All deaths in the CAPB trial occurred in patients >65 years. Monitor closely for clinical response.

Adverse Effects[1,2,3,4,5]**:**

>10%

Gastrointestinal:

Nausea (2-22%)

Vomiting (3-11%)

1-10%

Cardiovascular:

Hypertension (3%)

Insomnia (3%)
Atrial fibrillation (<2%)
Tachycardia (<2%)

Central Nervous System:

Headache (2-3%)
Fatigue (<2%)
Lethargy (<2%)
Vertigo (<2%)

Dermatologic:

Erythema (<2%)
Hyperhidrosis (<2%)
Pruritus (<2%)
Urticaria (<2%)

Endocrine & Metabolic:

Increased gamma-glutamyl transferase (3%)

Gastrointestinal:

Diarrhea (3%)
Constipation (2%)
Abdominal pain (<2%)
Dysgeusia (<2%)
Dyspepsia (<2%)
Increased serum lipase (<2%)
Oral candidiasis (<2%)

Genitourinary:

Vulvovaginal candidiasis (<2%)

Hematologic & Oncologic:

Anemia (<2%)
Thrombocythemia (<2%)

Hepatic:

Increased serum alanine aminotransferase (4%)
Increased serum aspartate aminotransferase (2-4%)
Increased serum alkaline phosphatase (<2%)
Increased serum bilirubin (<2%)

Hypersensitivity:

Hypersensitivity reaction (<2%)

Local:

Infusion site reaction (5%)

Neuromuscular & Skeletal:

Increased creatine phosphokinase (<2%)
Arrest of bone development AND/OR growth

Respiratory:

Oropharyngeal pain (<2%)

Other:

Death (2%)

Drug Interactions[1,2,3,4,5]:

Aminolaevulinic Acid

Photosensitizing agents may enhance the photosensitizing effect of aminolaevulinic acid. Avoid combination.

Anticoagulant Drugs & Vitamin K Antagonists (Warfarin)

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

Antacids and Iron Preparations

Absorption of oral tetracyclines, including omadacycline, is impaired by antacids containing aluminum, calcium, zinc, or magnesium, bismuth subsalicylate, and iron containing preparations. Separate administration by several hours when possible.

Bile Acid Sequestrants

May decrease the absorption of tetracyclines. Consider therapy modification.

Lactobacillus and Estriol

Antibiotics may diminish the therapeutic effect. Monitor therapy.

Lanthanum

May decrease the serum concentration of tetracyclines. Administer tetracyclines at least two hours before or after lanthanum.

Mecamylamine

Tetracyclines may enhance the neuromuscular-blocking effect of mecamylamine. Avoid combination.

Methoxyflurane

Tetracyclines may enhance the nephrotoxic effect of methoxyflurane. Avoid combination.

Mipomersen

Tetracyclines may enhance the hepatotoxic effect of mipomersen. Monitor therapy.

Multivitamins/Minerals

May decrease the serum concentration of tetracyclines. If co-administration of a polyvalent cation-containing multivitamin with oral tetracyclines cannot be avoided, separate administration by several hours.

Neuromuscular-Blocking Agents

Tetracyclines may enhance the neuromuscular-blocking effect of these agents. Monitor therapy.

Penicillins

Tetracyclines may diminish the therapeutic effect of penicillins. Consider therapy modification.

Porfimer & Verteporfin

Photosensitizing agents may enhance the photosensitizing effect of porfimer. Monitor therapy.

Quinapril

May decrease the serum concentration of tetracyclines. Separate doses of quinapril and oral tetracycline derivatives by at least two hours. Monitor for reduced tetracycline efficacy if these products are used together.

Retinoic Acid Derivatives

Tetracyclines may enhance the adverse/toxic effect. The development of pseudotumor cerebri is of particular concern. Avoid combination.

Sodium Picosulfate

Antibiotics may diminish the therapeutic effect. Consider using an alternative product for bowel cleansing prior to a colonoscopy. Consider therapy modification.

Strontium Ranelate

May decrease the serum concentration of tetracyclines. It is recommended that strontium ranelate treatment be interrupted during tetracyclines therapy. Avoid combination.

Sucralfate

May decrease the absorption of tetracyclines. Administer the tetracycline derivative at least two hours prior to sucralfate. Consider therapy modification.

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

CABP:

Loading dose: 200 mg IV over 60 minutes for 1 dose on day 1 OR 100 mg IV over 30 minutes for 2 doses on day 1; follow with 100 mg IV once daily or 300 mg PO once daily; treatment duration up to 14 days

Skin Infection:

IV loading dose: 200 mg IV over 60 minutes for 1 dose on day 1 OR 100 mg IV over 30 minutes for 2 doses on day 1; follow with 100 mg IV once daily or 300 mg PO once daily; treatment duration 7-14 days

Oral loading dose: 450 mg PO once daily on days 1 and 2; follow with 300 mg PO once daily; treatment duration 7-14 days (Note: oral dosing is based on unpublished OASIS 2 trial data[8])

Pediatrics

Safety and efficacy have not been established in patients younger than 18 years.

Elderly

Refer to adult dosing.

Renal impairment

Specific guidelines for dosage adjustments in renal impairment are not available. It appears that no dosage adjustments are needed.

Hepatic impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available. It appears that no dosage adjustments are needed.

Maximum Dosage Limits

Adults and Geriatric: 450 mg/day PO; 200 mg/day IV

Use in special circumstances:

Overdosage[1]**:** No specific information is available on the treatment of overdosage with omadacycline. Following a 100 mg single dose of IV administration, 8.9% of dose is recovered in the dialysate.

Reproductive Risk[1,2,3,4,5]**:** Female patients should be advised to use an acceptable form of contraception during treatment and to report suspected pregnancy right away. In rat studies, omadacycline affected fertility parameters in female rats, resulting in reduced ovulation and increased embryonic loss at intended human exposures. In male rat studies, injury to the testis and reduced sperm counts and motility occurred after treatment with omadacycline.

Conclusion:

Omadacycline is an effective therapy in the treatment of CABP and acute bacterial skin and skin-structure infections. The pharmacological profile is consistent with what is found in other tetracycline antibiotics. Future studies are still needed to truly assess its place in clinical practice. It is also important to note the cost differences between omadacycline and other antibiotics. IV omadacycline is cheaper than oral omadacycline ($300-400 per day). To compare, linezolid costs $10 per day[9]. Because it is only a once daily treatment, omadacycline could be an attractive alternative to other comparator antibiotics, but cost comparisons should be taken into consideration. In addition, the unpublished OASIS 2 trial that studied the oral dosing should also be taken into consideration. More published studies are needed to determine the safety and tolerability of the oral formulation.

Recommended References:

1. Nuzyra [package insert]. Boston, MA: Paratek Pharmaceuticals, Inc.: 2018.
2. Omadacycline. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: March 6, 2019.
3. Omadacycline. Lexi-Drugs [database online]. Lexi-Comp, Inc; Accessed March 6, 2019.
4. Omadacycline. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2019. Available at: http://www.clinicalpharmacology.com Accessed: March 6, 2019.
5. Omadacycline Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: March 6, 2019.
6. Stets R, Popescu M, Gonong JR, et al. Omadacycline for Community-Acquired Bacterial Pneumonia. *N Engl J Med.* 2019 Feb 7;380(6):517-527.
7. O'Riordan W, Green S, Overcash S, et al. Omadacycline for Acute Bacterial Skin and Skin-Structure Infections. *N Engl J Med.* 2019 Feb 7;380(6):528-538.
8. 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 Nov;56(11):5650-4.
9. Seeking Alpha Staff. Paratek Pharmaceuticals: The Realistic Case for Omadacycline. Updated March 10, 2018. Accessed on March 20, 2019. Available at: https://seekingalpha.com/article/4153599-paratek-pharmaceuticals-realistic-case-omadacycline.

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