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Omadacycline (Nuzyra) — A New Tetracycline Antibiotic .......................................................... p 74

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The FDA has approved omadacycline (Nuzyra – Paratek), a semisynthetic tetracycline derivative, for once-daily IV and oral treatment of community-acquired bacterial pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSIs) in adults.

**MECHANISM OF ACTION** — Omadacycline is an aminomethylcycline antibiotic that binds to the 30S subunit of the bacterial ribosome, inhibiting bacterial protein synthesis. It overcomes efflux and ribosomal protection mechanisms of resistance, the two primary mechanisms responsible for resistance to tetracyclines.

<table>
<thead>
<tr>
<th>Pronunciation Key</th>
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<tbody>
<tr>
<td>Omadacycline: oh mad’ a sye’ kleen</td>
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<tr>
<td>Nuzyra: new zye’ rah</td>
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**ACTIVITY** — Omadacycline has a broad spectrum of activity that includes gram-positive, gram-negative, atypical, and anaerobic pathogens (see CAP and ABSSSIs sections for specific clinical activity). It has been shown to have *in vitro* activity against some drug-resistant pathogens including penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE), beta-lactamase-positive *Haemophilus influenzae*, *Acinetobacter* species, and non-ceftazidime-susceptible and non-imipenem-susceptible Enterobacteriaceae, but it is not active against *Pseudomonas*, *Proteus*, *Morganella*, or *Providencia* species.¹⁻³

**CAP** — The organisms responsible for CAP are usually not confirmed, but *S. pneumoniae* and *Mycoplasma pneumoniae* are common causative pathogens.⁴ Other pathogens include *H. influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella* species, *Staphylococcus aureus*, and anaerobic mouth organisms. Some IV drugs for empiric treatment of CAP in hospitalized patients are listed in Table 2.

**Activity** — In CAP, omadacycline has been shown to have *in vitro* and clinical activity against *C. pneumoniae*, *Legionella pneumophila*, *M. pneumoniae*, *S. pneumoniae* (including tetracycline- and macrolide-resistant isolates), *S. aureus* (methicillin-resistant isolates), *H. influenzae*, *Haemophilus parainfluenzae*, and *Klebsiella pneumoniae*.

**Clinical Studies** — In a double-blind trial (OPTIC), 774 adults with CAP were randomized to receive initial IV treatment with omadacycline or moxifloxacin; patients could be switched to the respective oral formulation after 3 days to complete a total of 7-14 days of treatment. Omadacycline was noninferior to moxifloxacin in early clinical response rates and clinical response rates 5-10 days post-treatment (see Table 3).⁵
ABSSSIs – Purulent skin and soft-tissue infections are commonly caused by methicillin-resistant S. aureus (MRSA). For small abscesses, incision and drainage may be sufficient. Nonpurulent skin and soft-tissue infections (cellulitis/erysipelas) are often caused by beta-hemolytic streptococci. Some oral drugs for empiric treatment of ABSSSIs are listed in Table 4.

Complicated ABSSSIs, such as those that occur in patients with burns, diabetes, or traumatic or surgical wound infections, are often polymicrobial and should be treated with a broad-spectrum parenteral antibiotic, such as piperacillin/tazobactam or a carbapenem.6,7

Activity – In ABSSSIs, omadacycline has been shown to have in vitro and clinical activity against methicillin-susceptible and methicillin-resistant S. aureus, Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus group, Enterococcus faecalis, Enterobacter cloacae, and K. pneumoniae.

Clinical Studies – FDA approval of omadacycline for ABSSSIs (cellulitis/erysipelas, major cutaneous abscess, or wound infection, with a lesion size of ≥75 cm² and symptoms of systemic infection) was based on the results of 2 double-blind trials (see Table 5). In OASIS-1, 627 patients with ABSSSIs were randomized to receive initial IV treatment with omadacycline or linezolid; patients could be switched to the respective oral formulation after 3 days to complete a total of 7-14 days of treatment. Omadacycline was noninferior to linezolid in early clinical response rates and clinical response rates 7-14 days post-treatment.8

In OASIS-2, summarized in the package insert, 735 patients with ABSSSIs were randomized to receive omadacycline or linezolid orally for 7-14 days. Omadacycline was noninferior to linezolid in early clinical response rates and clinical response rates 7-14 days post-treatment.

Table 3. Omadacycline Clinical Trial Results for CAP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Early Clinical Response</th>
<th>Post-Treatment Clinical Response</th>
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<tbody>
<tr>
<td>OPTIC® (n=774)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omadacycline</td>
<td>81.1%*</td>
<td>86.7%*</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>82.7%</td>
<td>85.1%</td>
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</table>

*noninferior to moxifloxacin

1. Survival with improvement of one or more levels from baseline (measured on a 4-point scale) in at least 2 symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) and no worsening of symptoms at 72–120 hours after the first dose without use of rescue antibiotics; the primary endpoint.
2. Survival with resolution or improvement in symptoms to the extent that further antibiotic treatment was not necessary; a secondary endpoint. Evaluated up to 5-10 days post-treatment.
4. 100 mg IV every 12 hours x 2 doses, then 100 mg IV every 24 hours. Switch to oral omadacycline 300 mg once daily was allowed after 3 days of IV treatment.
5. 400 mg IV every 4 hours. Switch to oral moxifloxacin 400 mg once daily was allowed after 3 days of IV treatment.

ADVERSE EFFECTS – Omadacycline can cause nausea, vomiting, diarrhea, constipation, headache, hypertension, insomnia, and hepatic transaminase elevations. Nausea and vomiting are most likely to occur after taking an oral loading dose. Infusion-site reactions were reported with IV administration of the drug.

Tetracyclines, including omadacycline, can cause photosensitivity, pseudotumor cerebri, increased BUN, acidosis, hyperphosphatemia, and pancreatitis. They can also cause enamel hypoplasia, permanent tooth discoloration (more common with long-term use, but has been reported with repeated short courses of treatment), and reversible inhibition of bone growth; omadacycline should not be used in children ≤8 years old. Hypersensitivity reactions have been reported with omadacycline; the drug should not be used in patients with a history of a serious allergic reaction to any tetracycline.

Table 4. Some Oral Drugs for Empiric Treatment of ABSSSIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage</th>
<th>Cost²</th>
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<tbody>
<tr>
<td>TMP/SMX = generic</td>
<td></td>
<td></td>
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<tr>
<td>Bactrim DS (Sun)</td>
<td>1-2 DS tablets q12h</td>
<td>$1.20</td>
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<tr>
<td>Clindamycin⁴ – generic</td>
<td>300–450 mg PO q6-8h</td>
<td>10.70</td>
</tr>
<tr>
<td>Doxycycline – generic</td>
<td>100 mg PO bid</td>
<td>11.80</td>
</tr>
<tr>
<td>Vibramycin (Pfizer)</td>
<td>119.60</td>
<td></td>
</tr>
<tr>
<td>Linezolid⁵ – generic</td>
<td>600 mg PO bid</td>
<td>70.40</td>
</tr>
<tr>
<td>Zyvox (Pfizer)</td>
<td>2669.90</td>
<td></td>
</tr>
</tbody>
</table>

1. In outpatients.
2. Approximate WAC for 5 days’ treatment at the lowest usual adult dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. May 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
3. DS tablets contain trimethoprim 160 mg and sulfamethoxazole 800 mg.
4. An alternative regimen.

DRUG INTERACTIONS – Tetracyclines may reduce prothrombin activity, which could increase the risk of bleeding in patients taking an anticoagulant. Iron-containing products, bismuth subsalicylate, and antacids containing aluminum, calcium or magnesium can impair the absorption of oral tetracyclines, including omadacycline.

PREGNANCY AND LACTATION – In animal studies, administration of high doses of omadacycline during organogenesis was associated with embryofetal...
Effects on male fertility are unknown. Reduced sperm count and motility. Its long-term toxicity, congenital malformations, and reduced fetal weight. Tetracyclines, including omadacycline, can cause permanent discoloration of deciduous teeth and reversible inhibition of bone growth when used during the last 2 trimesters of pregnancy.

Tetracyclines are excreted in human breast milk. Breastfeeding is not recommended during treatment with omadacycline and for 4 days after the last dose.

In animal studies, administration of omadacycline reduced sperm count and motility. Its long-term effects on male fertility are unknown.

**DOSAGE, ADMINISTRATION, AND COST** — The recommended IV loading dose for treatment of CAP and ABSSSIs is 200 mg (over 60 minutes) once or 100 mg (over 30 minutes) twice on day 1, followed by maintenance treatment with 100 mg IV once daily. After the initial IV loading dose, patients can be switched to oral omadacycline 300 mg once daily. An all-oral regimen is approved for treatment of ABSSSIs: a loading dose of 450 mg once daily for 2 days, followed by a maintenance dose of 300 mg once daily. The FDA-approved treatment duration for both infections is 7-14 days.

Patients should fast for at least 4 hours before taking omadacycline tablets. No food or drink (except water) should be consumed for 2 hours after and no dairy products, antacids, iron supplements, or multivitamins should be taken for 4 hours after taking omadacycline.

The cost of a 7-day supply of omadacycline is $2415 for the IV formulation and $2765 for the oral tablets.9

**Summary: Omadacycline (Nuzyra)**

- Semisynthetic tetracycline antibiotic
- FDA-approved for IV and oral treatment of community-acquired bacterial pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSIs) in adults
- Broad spectrum of activity against gram-positive, gram-negative, atypical, and anaerobic organisms
- Not active against *Pseudomonas, Proteus, Morganella,* or *Providencia* species
- In vitro activity against some drug-resistant pathogens, but clinical data are limited
- Noninferior to moxifloxacin for treatment of CAP and to linezolid for treatment of ABSSSIs
- Nausea and vomiting are common with the oral formulation
- Fasting required at least 4 hours before and 2 hours after taking the oral tablets
- Should not be used first-line for empiric treatment of CAP or ABSSSIs

**CONCLUSION** — Omadacycline (Nuzyra), a new broad-spectrum tetracycline antibiotic, is effective for IV and oral treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections in adults. It is active in vitro against some multi-drug-resistant pathogens, but clinical data supporting its effectiveness for such use are lacking. Omadacycline should be reserved for patients who cannot take other antibacterial drugs or for those with infections caused by resistant pathogens for which there are no effective alternatives. It should not be used for empiric treatment of community acquired pneumonia or acute bacterial skin and skin structure infections.

9. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: Analysource® Monthly. May 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.