CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209816Orig1s000
209817Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209816 and 209817
PDUFA Goal Date	October 2, 2018
OSE RCM #	2017-2606 and 2017-2608
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	August 23, 2018
Subject	Evaluation of Need for a REMS
Established Name	Omadacycline
Trade Name	Nuzyra
Name of Applicant	Paratek Pharma, LLC
Therapeutic Class	Semisynthetic aminomethylcycline related to tetracycline
Formulation(s)	150 mg tablet (NDA 209816) and 100 mg vial (NDA 209817)
Dosing Regimen	200 mg intravenously (IV) on day 1, then 100 mg IV once daily or 300 mg orally once daily; or 450 mg orally once daily for 2 days, then 300 mg orally once daily for a total 7 to 14 days.

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity omadacycline is necessary to ensure the benefits outweigh its risks. Parateck Pharma, LLC (Parateck) submitted a New Drug Application (NDA) 209816 (oral tablet) and 209817 (intravenous vial) for omadacylcine with the proposed indication for the treatment of [redacted] (b) (4) with the following infections caused by susceptible microorganisms:

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

There was mortality imbalance in the CABP trial, higher mortality (2%) was observed in omadacycline treated patients as compared to the comparator (1%). The cause of the imbalance has not been established. All deaths occurred in patients older than 65 years of age, with greater disease severity and chronic comorbid medical conditions. This serious risk is communicated in the [redacted] (b) (4) Warnings and Precautions section of labeling. A post approval study in CABP to obtain additional safety and efficacy data [redacted] (b) (4) is currently under discussion between the FDA and the applicant.

Omadacycline is structurally similar to tetracycline-class antibiotics. Other serious risks associated with omadacyclineare are similar to the risks in the tetracycline class and include tooth development and enamel hypoplasia, inhibition of bone growth, hypersensitivity reactions, Clostridium difficile infection, tetracycline class effects, development of drug-resistant bacteria, [redacted] (b) (4) . These risks will be conveyed in the Warnings and Precautions section of labeling.

The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Anti-Infective Products (DAIP) agree that a REMS is not needed to ensure the benefits of omadacycline outweigh its risks. Omadacyclinne belongs to a new class of compounds called aminomethlcyclines, which are semisynthetic derivatives related to the tetracycline class. A REMS has not been required for the tetracycline class of antibiotics, the primay risk mitigation has been through labeling. The risks of omadacycline will be communicated in the labeling, as is the case for other tetracyclines.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) omdacylcine is necessary to ensure the benefits outweigh its risks. Parateck submitted a New Drug Application (NDA) 209816 (oral tablet) and 209817 (intravenous vial) for omadacycline with the proposed indication for the treatment of adult patients with ABSSSI and CABP. This application is under review in the Division of Anti-Infective Product (DAIP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Omadacycline, a new molecular entity[a], is an antibacterial agent that belongs to a new class of compounds, namely the aminomethlcyclines, which are semisynthetic derivatives related to the tetracycline class. Omadacylcine, like other tetracyclines, exerts its antibacterial effect by binding to the 30S subunit of the bacterial ribosome, inhibiting the binding of aminoacyl transfer ribonucleic acid, and thereby blocking protein synthesis. Omadacycline is shown to be active in vitro against most gram-positive pathogens (e.g., Streptococcus pneumoniae and Staphylococcus aureus). It also exhibits in vitro activity against atypical pathogens (e.g., Legionella penumophila), and some anaerobic and gram-negative pathogen, including Haemophilus influenza. Omadacycline carries an aminomethyl moiety attached to the 9-position of minocycline and is active in vitro against gram positive bacteria expressing tetracycline resistance active efflux pumps and ribosomal protection proteins. In general, omadacycline is considered bacteriostatic; however, omadacylcine has demonstrated bactericidal activity against some isolates of S. pneumoniae.

Omadacycline is proposed as a once daily, broad spectrum antibiotic, with both intravenous (IV) and oral formulations, for the treatment of adult patients with CABP and ABSSSI. The recommended dosage for CABP is 200 mg adminsered IV as a first dose (or 100 mg (b) (4) IV for the first 2 doses), followed by 100 mg IV once daily or 300 mg administered orally once daily. The recommended dosage for ABSSSI is the same as CABP. If oral only treatment is initiated for ABSSSI, the recommended dosage is 450 mg orally once a day for the first 2 days, followed by 300 mg once daily. The oral only regimen is not recommended for the treatment of CABP. Treatement duration is 7 to 14 days for both ABSSSI and CABP. Omadacycline was designated as a Qualified Infectious Disease Products (QIDP) and Fast Track review. Omadacycline is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for omadacycline relevant to this review:

- December 5, 2012: QIDP designation for NDA 209817 (IV formulation) granted.
- March 21, 20103: QIDP designation for NDA 209816 (oral formulation) granted.
- November 2, 2015: Fast track designation granted
- December 21, 2017: NDA 209816 and 209817 submissions received

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

- May 18, 2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for omadacylcinesas
- August 8, 2018: Antimicrobial Drugs Advisory Committee (AMDAC) Meeting was convened to discuss:
    1. Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of ABSSSI?
        a. If yes, please provide any recommendations concerning labeling.
        b. If no, what additional studies/analyses are needed?
    2. Has the applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of CABP?
        a. If yes, please provide any recommendations concerning labeling.
        b. If no, what additional studies/analyses are needed?

    The AMDAC voted 17/1 in favor for ABSSSI and 14/4 in favor for CABP. Eight deaths were seen among CABP patients that received omadacycline versus 3 with its comparator moxifloxacin in a phase 3 trial. A REMS proposal was not discussed or recommended by the Committee.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Community-acquired bacterial pneumonia (CABP):

CABP is a common and potentially serious illness. It is associated with considerable morbidity and mortality,[b] particularly in older patients and those with significant comorbidities.[1] Influenza/pneumonia is the eighth leading cause of death in the United States (US) in 2015 and 2016, [2] accounting for over 4 million healthcare office visits.[c] It is estimated that each year over 5 million cases occur in the US with over 1 million hospitalizations and 60,000 deaths from pneumonia. Typically, about 80% of these cases are treated as outpatients and 20-25% in the hospital setting.[3] Mortality rate secondary to pneumonia have not decreased despite advanced in medical treatment. This observation is attributed to an increase in populations at highter risk for morbidity and mortality such as the elderly and immunocompromised and emergence of resistant organisms. Therefore, there is a need to develop new antibacterials to treat CABP.

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Acute bacterial skin and skin structure infections (ABSSSIs):

ABSSSIs, formerly called complicated skin and skin structure infection (cSSSIs), are among the most common infections encountered in clinical practice. The 2013 FDA Guidance for Inducstry (ABSSSIs: Developing Drugs for Treatment) defines an ABSSSI as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration). These infections are subdivided into the following categories: cellulitis/erysipelas, wound infection, and major cutaneous abscess.[4] There is a wide clinical spectrum of ABSSSIs, from mild, superficial infections to life-threatening conditions affecting deeper tissure layer that leads to hospitalization. ABSSSIs have placed an increasing burden on healthcare systems globally. This burden is due to the initial increased spread and subsequent persistence of methicillin-resistant Staphlococcus aureus (MRSA) in some regions. [5] Staphlococcus aureus infections are usually treated with methicillin based antibacterials, but drug resistance has become increasingly common, with approximately 60% of inpatients infections thought to be methicillin resistant.[6] The continuing increase in antibacterial resistance in US remains a concern.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Community-acquired bacterial pneumonia (CABP):

The currently avialble treatments approved by the FDA include the following pharmacologic classes of antibacterials, along with specific drug products:

- Cephalosporins (cefepime, cefotaxime, ceftriaxone, cefuroxime)
- Penicillins with beta-lactamase inhibitors (ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate)
- Macrolides (azithromycin, clarithromycin)
- Quinolones (Gemifloxacin, levofloxacin, moxifloxacin)
- Carbapenems (ertapenem, meropenem).

Acute bacterial skin and skin structure infections (ABSSSIs):

Per Infectious Disease Society of America (IDSA) 2014 guidleine,[7] the following antibiotics have been used to treat ABSSIs:

Nonpurulent:

- mild: oral penicillin VK, cephalosporin, dicloxacillin, clindamycin.
- moderate: intravenous penicillin, ceftriaxone, cefazolin, clindamycin

- severe:
    1. empiric therapy: vancomycin +pipieracillin/tazobactam
    2. defined therapy: penicillin+clindamycin, doxycycline+ceftazidime, doxycycline+ciprofloxacin, vancomycin+piperacillin/tazobactam

Purulent:

- mild: incision & drainage (I & D)
- moderate: I & D plus
    1. empiric therapy: trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline
    2. defined therapy: MRSA: TMP/SMX; MSSA: dicloxacillin or cephalexin
- severe: I & D plus
    1. empiric therapy: vancomycin, daptomycin, linezolid, telavancin, ceftaroline
    2. defined therapy: MRSA: see empiric; MSSA: nafcillin, cefazolin, clindamycin

4 Benefit Assessment

The clinical and statistical reviewers concluded in the FDA briefing document[8] that the trial demonstrated robust efficacy results [d] for the treatment of CABP and ABSSSI.

CABP:

A total of 774 adults with clinically and radiologically confirmed CABP were randomized in a multinational, double-blind, double-dummy, non-inferiority trial (Trial 1, NCT#02531438) comparing 7-14 days of omadacycline versus moxifloxacin. The clinical and statistical reviewers concluded that the trial demonstrated robust efficacy results.[9] [e]

Trial 1 compared 386 patients on omadacycline arm (100 mg IV every 12 hours for 2 doses on day 1, followed by 100 mg IV, or 300 mg orally, daily) to 388 patients on moxifloxacin arm (400 mg IV or orally daily) in the treatment of CABP. Patients could not switch to oral therapy until day 4. Fifty-five percent of patients were male and 92% of patients were white. Majority (60%) of patients in each group belonged to Pneumonia Outcomes Research Team (PORT) Risk III, and over 25% to PORT Risk class IV;

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

PORT risk class II was limited to 14% in each group. The median age was 62 and common comorbid conditions included hypertension, diabetes mellitus, chronic lung disease, coronary artery disease, and atrial fibrillation.

Efficacy was assessed at early clinical response (ECR), 72-120 hours after the first dose. A clinical success at ECR was defined as survival with improvement in at least 2 of 4 symptoms (cough, sputum production, chest pain, dyspnea) without deterioration in any of these 4 symptoms in the intent to treat population (ITT), which consisted of all reandomized patients (see table 1).[10]

Table 1: Efficacy evaluation in CABP Trial (ITT population)

Endpoint	Omadacycline	moxifloxacin	Treatment difference (95% confidence interval)
Early clinical responce	81.1%	82.7%	-1.6 (-7.1, 3.8)

Successful clinical response was also assessed by the investigator at the post therapy evaluation (PTE, 5-10 days after last dose of study drug) visit and defined as survival and improvement in signs and symptoms of CABP to the extent that further antitiotics is not necessary. Table 2 presents the results of clinical response at PTE. Clinical response rates were also evaluated by most common pathogen in microbiological-ITT population (micro-ITT), which coniststed of all randomized pateints with causative pathogen identified as baseline and presented in table 2.

Table 2: Secondary efficacy endpoint in CABP Trial (ITT population)

endpoint	omadacylcine	moxifloxacin	Treatment difference (95% confidence interval
Clinical success at PTE	87.6%	85.1%	2.5 (-2.4, 7.4)

ABSSSI:

A total of 1390 alduts with ABSSSIs were randomized in 2 multicenter, multinational, double-blind, double-dummy non-inferiority trials (Trial 1, NCT#02378480 and Trial 2, NCT#02877927). Both trials compared 7-10 days of omadacycline versus linezolid. Paitents with cellulitis, major abscess, or wound infection were enrolled in the trials.

In trial 1, 329 patients were randomized to omadacylcine (100 mg IV every 12 hours for 2 doses followed by 100 mg IV every 24 hours, with the option to switch to 300 mg orally every 24 hour) and 326 patients were randomized to linezolid (600 mg IV every 12 hours, with the option to switch to 600 mg orally every 12 hours). After an initial 3 days of IV theray, patients could be switched to oral therapy at the physician's discretion. Patients in the trial had the following infections: cellulitis (38%), wound infectin (33%), and major abscess (29%). The mean age was 47 years.

In trial 2, 368 patients were randomized to omadacycline (450 mg oral once daily on days 1 and 2, followed by 300 mg orally once a day) and 367 patients were randomized to linezolid (600 mg orally every 12 hours). Patients in the trial had cellulitis (33%), wound infection (59%), and major abscess (18%). The mean age was 44 years.

Efficacy for both trials was assessed at the Early Clinical Response (ECR) of the infection. Clinical success at ECR was defined as ≥20% reduction in lesion size in the mofdified intent-to-treat population (mITT) within 48-72 hours after first dose (see Table 3). The mITT population was defined as all reandomized subjects without a sole Gram-negative causative pathogen at screening.

Table 3: Clinical response rates at ECR in phase 3 ABSSSI Trials (mITT population)

	Omadacylcine	Linezolid	Treatment difference (2-sided 95% Confidence Interval)
Trial 1	84.8%	85.5%	-0.7 (-6.3, 4.9)
Trial 2	87.5%	82.5%	5.0 (-0.2, 10.3)

Clinical response at the post therapy evaluation (PTE, 7-14 days after last dose) visit was defined as survival after completion of study treatment without receiving any alternative antiobiotics other than study drug, without unplanned major surgical intervention, and sufficient resolution of infection such that further antitiotics is not needed (see table 4) . Clinical response reates at PET by most common pathogen was evaluated in the microbiological -mITT population, which consisted of patients in mITT who had a baseline gram-posive causative pathogen identified at baseline.

Table 4: Clinical response rates at PTE in phase 3 ABSSSI Trials (mITT population)

	Omadacyline	linezolid	Treatment difference (2-sided 95% CI)
Trial 1	86.1%	83.6%	2.5 (-3.2, 8.2)
Trial 2	84.2%	80.8%	3.3 (-2.2, 8.9)

5 Risk Assessment & Safe-Use Conditions

In the clinical trail for the treatment of CABP, there were more deaths within 30 days from the time of enrollment in omadacylcine-treated pateints compared to those treated with moxifloxacin, the control antibacterial drug in the trial. A total of 8 deaths (2%) occurred in omadacycline treated pateitns compared to 3 deaths (1%) in pateints treated with moxifloxacin. The concern of imbalance in the death

rate in the CABP trial [f] was brought to the AMDAC meeting on August 8, 2018. Most committee members shared the concern about the potential increased risk, but some also suggested that deaths were to be expected among CABP patients and were reassured that there was no common mechanism among the deaths reported. The FDA indicated that mortality rates seen were in line with other randomized trials conducted in CABP. Also the FDA suggested the risk factors for mortality appeared to be a PORT risk class IV rating, age older than 65, underlying chronic obstructive pulmonary disease, asthma or emphysema, and diabetes mellitus. Nearly all members suggested a postmarketing trial to answer the mortality questions as well as gather more information on specific subgroups, including those with bacteremic pneumonia and individuals with higher PORT scores. The serious risks associated with omadacycline are described in the section below and, if approved, will be communicated in the Warnings and Precautions section of the label.

5.1 Mortality imbalance in the CABP trial

In the clinical trail for the treatment of CABP, there were more deaths within 30 days from the time of enrollment in omadacylcine-treated pateints compared to those treated with moxifloxacin, the control antibacterial drug in the trial. A total of 8 deaths (2%) occurred in omadacycline treated pateitns compared to 3 deaths (1%) in pateints treated with moxifloxacin. The cause of the imbalance in mortality outcomes has not been established. Prescribers will be advised to (b) (4)

5.2 Tooth development and enamel hypoplasia

The use of omadacycline during tooth development 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. A recommendation for prescribers will be included to advise patients of the potential risk to the fetus if omadacycline is used during the second or third trimester of pregnancy.

5.3 Inhibition of bone growth

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 infibula growth ratge has been observed in premature infancts given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. A recommendation for prescribers to advise patients

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

of the potential risk to the fetus if omadacycline is used during the second or third trimester of pregnancy.

5.4 Hypersensitivity reactions

Hypersensitivity reactions have been reported with omadacycline. Life-threatening hypersensitivity (anaphylactic) reactions have been reported with other tetracycline class antibiotics. Omadacycline is structurally similar to other tetracycline class antibiotics and is contraindicated in patients with known hypersensitivity to tetracycline class antibiotics. Prescribers will be advised to discontinue omadacycline if an allergic reaction occurs.

5.5 Clostridium difficile infection

Clostridum difficile associated diarrhea (CDAD) has been reported with use of nearly all antibiotics, and may range in severity from mild diarrhea to fatal colitis. 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 antibiotics therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotics use. If CDAD is suspected or confirmed, ongoing antibiotics use not directed against C.difficile may need to be discontinued. The label will include recommendations for appropriate fluid and electrolyte management, protein supplementation, antibacterial drug therapy of C. difficile, as well as surgical evaluation,as clinically indicated.

5.6 Tetracycline-class effects

Omadacycline is structurally similar to teracycline class antibiotics and may have similar adverse effects. Adverse reactions including photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased BUN, azotemia, acidosis, hyperphosphatemia, and pancreatitis have been reported for other tetracycline-class antitiotics, and may occur with omadacycline. Prescribers will be advised to discontinue omadacycline if any of these adverse reactions are suspected.

5.7 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.

6 Expected Postmarket Use

According to the current propsed indication, if approved, omadacycline will be used both in inpatient and outpatient (such as infusion centers or home infusion) settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for omadacycline beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of omadacycline on the basis of the efficacy and safety information currently available. [11]

There was mortality imbalance in the clinical trial for the treatment of CABP, 8 deaths (2%) in patients randomized omadacycline versus 3 deaths (1%) in patients randomized to the comparatory drug. All deaths occurred in patients who had greater disease severity and had chronic comorbid medical conditions at baseline. The cause of the imbalance in mortality outcomes has not been established. All deaths occurred in patients who were older than 65 years of age, had a baseline score on a pneumonia severity scoring system indicating higher disease severity (e.g. risk class III or IV on the PORT Risk classification) and in patients who had chronic co-morbid medical conditions such as underlying chronic lung dsease, chronic heart disease, or diabetes emllitus. If approved, the product label will advise prescribers to (b) (4) . A postmarketing study to answer the mortality questions (b) (4) is being negotiated between the FDA and the applicant.

Omadacycline is structurally similar to tetracycline-class antibiotics. Life-threatening hypersensitivity reactions have been reported with other tetracycline antibiotics. If approved, this safety issue will be communicated in the Contraindications and Warnings and Precautions section of the label. If approved, the other adverse reactions including tooth development and enamel hypoplasia, inhibition of bone growth, C. difficile infection, tetracycline-class effects, development of drug-resistant bacteria, (b) (4) will be conveyed in the Warnings and Precautions section of labeling.

Vibativ (telavancin) is a semisynthetic derivative of vancomycin and a first-in-class lipoglycopeptide antibacterial drug that was approved in 2009 for the treatment of complicated skin and skin structure infections (cSSSI). At the time of approval the FDA determined that Vibativ was required to have a REMS to address the risk teratogenicity. The REMS for Vibativ consisted of a Medication Guide and Communication Plan with the goal of avoiding unintended exposure of pregnant women to Vibativ. In 2013, a new indication for Vibativ was added for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). The REMS was modified to address the risk of increased mortality in patients with pre-existing creatinine clearance of ≤ 50 ml/min being treated for HABP/VABP. In March 2017, based on the status of the CP activities, the REMS assessment findings (the goals of the

REMS have been met),[12] and available safety data, the REMS for Vibativ was released. A Boxed Warning and Medication Guide as part of labeling are used to communicate the risks.

Omadacyclinne belongs to a new class of compounds called aminomethlcyclines, which are semisynthetic derivatives related to the tetracycline class. A REMS has not been required for the tetracycline class of antibiotics, the primay risk mitigation has been through labeling. The risks of omadacycline will be communicated in the labeling, as is the case for other tetracyclines.

9 Conclusion & Recommendations

Based on the clinical review, this reviewer agrees that the benefit-risk profile is favorable, therefore, a REMS is not necessary for omadacycline to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Marrie TJ and File TM. Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults. UpToDate, accessed June 6, 2018

[2] www.cdc.gov/hiv/statistic/overview/index.html accessed June 6, 2018

[3] FDA briefing document for omadacycline for the meeting of AntiMicrobial Drug Adivisory Committee August 8, 2018

[4] US FDA, Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. www.fda.gov/downloads/drugs/guidances/ucm071185.pdf published October 2013, accessed June 6, 2018

[5] Pulido-Cejudo, A, Guzman-Gutierrez M, et al. Management of acute bacterial skin and skin structure infections with a focus on pateints at high risk of treatment failure. Ther Adv Infect Dis. 2017 Sep; 4(5): 143-161

[6] National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control. 2004 Dec; 32(8): 470-85

[7] Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America, www.idsociety.org/guidelines/patient_care, accessed June 6, 2018

[8] FDA briefing document for Meeting of the Antimicrobial Drug Advisory Committee, August 8, 2018

[9] Rashid, M and Kapoor, R Division of Anti-Infective Products, mid-cycle presentation, May 8, 2018

[10] Omadacycline draft prescribing information, August 17, 2018

[11] Rashid, M and Kappor, R Division of Anti-Infective Products, mid-cycle presentation, May 8, 2018

[12] Olickal T, REMS modification review of VIbativ, in DARRTS March 9, 2017

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/s/

MEI-YEAN T CHEN
08/23/2018

ELIZABETH E EVERHART
08/23/2018
I concur

CYNTHIA L LACIVITA
08/23/2018
Concur