FDA Introductory Comments

NDAs 209816, 209817

Omadacycline injection and tablets

Antimicrobial Drugs Advisory Committee Meeting

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FDA

Introduction

- NDAs 209816, 209817: Omadacycline tosylate injection and tablet
- Applicant: Paratek Pharmaceuticals, Inc.
- Qualified Infectious Disease Product (QIDP) designation for:
  - Community-acquired bacterial pneumonia (CABP)
  - Acute bacterial skin and skin structure infections (ABSSSI)
  - Uncomplicated urinary tract infections
- NDAs were granted priority review as the product has QIDP designation

Proposed Indications

- CABP caused by the following Gram positive, Gram negative, and atypical microorganisms:
  - *Streptococcus pneumoniae* (penicillin susceptible and resistant isolates, macrolide susceptible and resistant isolates and tetracycline susceptible- and resistant isolates), including cases with concurrent bacteremia, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*

- ABSSSI caused by the following Gram positive and Gram negative microorganisms:
  - *Staphylococcus aureus* (methicillin susceptible and resistant isolates), including cases with concurrent bacteremia, *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus grp*. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus mitis*, *Enterococcus faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Clostridium perfringens*, *Prevotella denticola*, *Prevotella melaninogenica*, and *Finegoldia magna*

Proposed Dose

Loading Dose	Maintenance Dose
Intravenous: 200 mg infused over 60 minutes on the 1st day OR 100 mg infused over 30 minutes, twice on the 1st day	100 mg IV once daily infused over 30 minutes or 300 mg orally once daily
Oral: 450 mg once a day on the 1st and 2nd day	300 mg orally once daily

Duration of therapy: 7-14 days

Development Program

- Two phase 3 trials in adults with ABSSSI (ABSI-1108 and ABSI-16301)
- One phase 3 trial in adults with CABP (CABP- 1200)
- Legacy Phase 2 study and a truncated Phase 3 trial in complicated skin and skin structure infections
- ABSI-1108 and CABP-1200 allowed for switch from IV to oral omadacycline; ABSI-16301 evaluated oral omadacycline

Phase 3 ABSSSI Trials

- Randomized, double-blind noninferiority (NI) trial comparing omadacycline to linezolid
- Trial design generally consistent with the ABSSSI guidance
- After a minimum of 3 days of blinded IV therapy, option to switch to oral therapy in ABSI-1108
- Primary analysis population: Modified intent-to-treat (mITT) population
- Primary endpoint: Early clinical response (ECR); ≥ 20% reduction in lesion size by 48-72 hours after initiating therapy
- Pre-specified NI margin of 10%

https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf

Efficacy Results

- In both trials, omadacycline was noninferior to linezolid for the ECR endpoint; pre-specified noninferiority margin was met
- Consistent results were seen for the key secondary endpoint of clinical response at the post-treatment evaluation, 7-14 days after the last dose of the treatment
- Consistent results also seen in subgroups of interest

Phase 3 CABP Trial

- Randomized, double-blind noninferiority (NI) trial comparing omadacycline to moxifloxacin
- Trial design generally consistent with the CABP guidance
- After a minimum of 3 days of blinded IV therapy, option to switch to oral therapy
- Primary analysis population: Intent-to-treat (ITT) population
- Primary endpoint: Early clinical response (ECR); 72-120 hours after initiating therapy based on improvement in symptoms (cough, sputum production, pleuritic chest pain, and dyspnea)
- Pre-specified NI margin of 10%

Efficacy Results

Outcome	Treatment Arm		Treatment Difference % 95% CI
	Omadacycline N=386	Moxifloxacin N=388	
Clinical Success	313 (81.2%)	321 (82.7%)	-1.6 (-7.1, 3.8)
Clinical Failure	73 (18.9%)	67 (17.3%)	

Indeterminate=Clinical failure
CI=Confidence intervals

Efficacy Results

- Key secondary endpoint: Investigator assessment at the post treatment evaluation visit (5-10 days after last treatment day); clinical success was similar between treatment groups
- 30-day all cause mortality was higher in the omadacycline arm (8/386, 2.1%) compared to the moxifloxacin arm (3/388, 0.8%)
- Subgroup analyses showed numerically lower response rates in patients > 65 years of age, PORT Class IV

PORT: Patients Outcomes Research Team

Safety Assessment

- No significant differences in adverse events were seen between treatment groups
- Nausea and vomiting reported with oral omadacycline
- Infusion site reactions (extravasation) reported with IV omadacycline in the ABSSSI trial
- An imbalance in 30 day all-cause mortality seen in the CABP trial

Outline for the Day

- Presentations by the Applicant
  - Clarifying questions
- Presentation by the FDA
  - Joseph Toerner MD MPH; Efficacy and Safety
  - Clarifying questions
- Open public hearing
- Questions for the committee

Question 1

- Has the Applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of acute bacterial skin and skin structure infections?
  - If yes, please provide any recommendations for labeling.
  - If no, please discuss additional studies/analyses that are needed.

Question 2

- Has the Applicant provided substantial evidence of the safety and effectiveness of omadacycline for the treatment of community acquired bacterial pneumonia?
  - If yes, please provide any recommendations for labeling.
  - If no, please discuss additional studies/analyses that are needed.


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