CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208385Orig1s000

STATISTICAL REVIEW(S)

REV-BIOMETRICS-02 (Review Noted (NAI))
NDA-208385
ORIG-1
Supporting Document 16
Resubmission/Class 2
Submit Date: 03/24/2017 - FDA Received Date: 03/24/2017

NAI for NDA resubmission of a daptomycin formulation. The resubmission mainly relates to product quality issues, and also contains responses to previous FDA comments on formatting of prescribing information and literature-based safety updates.

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/s/

DANIEL B RUBIN
03/28/2017

KAREN M HIGGINS
04/03/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208385
Drug Name:	Daptomycin for injection 350 mg per vial
Indication(s):	Complicated skin and skin structure infections
	Staphylococcus aureus bloodstream infections
Applicant:	Sagent Pharmaceuticals Inc.
Date(s):	Stamp date: August 25, 2015
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Daniel Rubin, PhD
Concurring Reviewers:	Statistical team leader: Karen Higgins, ScD
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Clinical reviewer: Alma Davidson, MD
	Clinical team leader: Hala Shamsuddin, MD
Project Manager:	Naseya Minor, MPH

1 SUMMARY

Daptomycin is an antibacterial drug in the cyclic lipopeptide class with *in vitro* activity against certain Gram-positive bacterial pathogens. It is FDA-approved for the treatment of complicated skin and skin structure infections (cSSSI), which are now known as acute bacterial skin and skin structure infections (ABSSSI). It is also FDA-approved for bloodstream infections (BSI) due to *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), including in patients with right-sided infective endocarditis. The FDA approvals were respectively based on evidence from two Phase 3 cSSSI trials and one Phase 3 BSI trial. The drug is administered intravenously and is supplied in single-use vials containing 500 mg daptomycin as a powder.

(b) (4)

This is a 505(b)(2) NDA submission in which the Applicant, Sagent Pharmaceuticals Inc., proposes to market a new formulation of daptomycin using the Agency's previous finding of safety and efficacy for the Reference Listed Drug (RLD) Cubicin®, which is the FDA-approved 500 mg/vial daptomycin formulation. The Applicant claims that its daptomycin for injection 350 mg/vial formulation (b) (4) to that of Cubicin® except for the amount of drug in the vial. The proposed dosage and administration will be identical to that of the RLD, which is either 4 mg/kg or 6 mg/kg depending on the patient's creatinine clearance. A physician would simply have to use a different number of vials of daptomycin powder to achieve the dose using the new product.

The Applicant has not performed any clinical studies of daptomycin for injection 350 mg/vial and does not propose any changes to the Indications and Usage or Clinical Studies section of the RLD label.

This NDA submission does contain a literature review of both the safety and efficacy of daptomycin. However, the submitted efficacy literature consists of a mixture of case reports, retrospective studies, and non-randomized comparisons. This reviewer did not consider this literature to constitute adequate and well-controlled investigations providing substantial evidence for or against the efficacy of daptomycin for the treatment cSSSI and BSI.

This reviewer defers to the Medical Officer and (if necessary) the Office of Surveillance and Epidemiology to determine if any new safety reports submitted in this application may affect the benefit-to-risk profile for daptomycin therapy. The Applicant's review of safety included a summary of daptomycin 500 mg/vial-related adverse event reports from the published literature as well as from the FDA Adverse Event Reporting System (AERS) from the second, third, and fourth quarters of 2014. Published literature and AERS data for the RLD have been available

[1] Pertel PE, Bernardo P, Fogarty C, Matthews P, Northland R, Benvenuto M, Thorne GM, Luperchio SA, Arbeit RD, Alder J. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clinical Infectious Diseases* 2008;46:1142-1151.
[2] Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *The Journal of Infectious Diseases* 2005;191(12):2149-2152.

since the 2003 approval, but the Applicant's timeframe was chosen to include newly available data between the most recent update to the RLD Prescribing Information (November 2014) and the time of analysis (June 2015). The Applicant's conclusion in its summary of clinical safety was that "No significant new adverse events were reported in the AERS search and literature searches performed" and thus that "no new safety information needs to be added to the Cubicin® Prescribing Information."

Overall, this reviewer has no statistical comments regarding this submission and defers to the other respective review disciplines.

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/s/

DANIEL B RUBIN
11/19/2015

KAREN M HIGGINS
11/20/2015
I concur.