CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208083Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Dorota Matecka, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	208083
Applicant	Celerity Pharmaceuticals, LLC
Date of Submission	June 30, 2016
PDUFA Goal Date	April 28, 2017
Proprietary Name / Established (USAN) names	Clindamycin in 0.9% Sodium Chloride Injection * (clindamycin phosphate)
Dosage forms/Strength	Intravenous Solution, 300 mg/50 mL, 600 mg/50 mL, 900 mg/50 mL
Proposed Indication(s)	• Serious infections caused by susceptible anaerobic bacteria • Infections Due to Susceptible Strains of Streptococci, Pneumococci and Staphylococci • Lower Respiratory Tract Infections • Skin and Skin Structure Infections • Gynecological Infections • Intra-abdominal Infections • Septicemia • Bone and Joint Infections
Recommended:	***Approval***

** No proprietary/trade name was proposed for the drug product*

1. Introduction

This 505(b)(2) NDA provides for a new injectable formulation of clindamycin to be used for the treatment of the same infections as listed in the listed drug labeling. The listed drug for this 505(b)(2) NDA is CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose) in the GALAXY plastic containers (300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL) approved under NDA 50639 in 1989 (and held by Pfizer). The currently proposed drug product is a new formulation of clindamycin injection, and differs from the listed drug in the excipients used in the formulation; specifically, the tonicity adjuster, i.e., 0.9% w/v sodium chloride versus 5% w/v dextrose used in the formulation of the listed drug. The currently proposed drug product is also supplied in the GALAXY containers.

No clinical data have been submitted in this NDA as the Applicant is relying on previous findings of efficacy and safety for the listed drug. The majority of the information submitted in the NDA relates to the chemistry, manufacturing and controls used in the manufacture of the proposed clindamycin drug product. In view of the similarities between the proposed and the listed drugs, a biowaiver for conducting in-vivo bioequivalence studies was requested by the Applicant.

2. Background

Clindamycin is a lincosamide antibacterial indicated for the treatment of several serious infections. Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is bacteriostatic.

There are a number of clindamycin drug products approved in the U.S., which include injectable formulations such as the listed drug, CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose). As discussed above, the drug product proposed by Celerity Pharmaceuticals contains the same drug substance but the drug product formulation differs from the listed drug in the tonicity adjuster, an excipient change that is not permitted per 314.94(a)(9)(iii)) for an injectable drug product. Therefore, this application was submitted as 505(b)(2) application and not as a 505(j) application.

3. Product Quality

The Product Quality Team from the Office of Pharmaceutical Quality (OPQ) included the following individuals:

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	Branch I/DNDAPI
Drug Product	Suresh Pagay Yushi Feng	Branch III/DNDP I
Process	Masihuddin Jaigirdar	Branch VII/DPA
Microbiology	Lisa Shelton	Branch II/DMA
Facility	Wenzheng (Wendy) Zhang	Branch II/DIA
Biopharmaceutics	Kaushalkumar Dave	Branch I/ DBP
Environmental Analysis (EA)	Suresh Pagay	Branch III/DNDP I
Regulatory Business Process Manager	Luz Rivera	Branch I/DRBPM I
Application Technical Lead	Dorota Matecka	Branch III/DNDP I

The chemistry manufacturing and controls information for clindamycin phosphate drug substance has been provided via a reference to DMF Type II (b) (4) . DMF (b) (4) has been found to be adequate via a chemistry review dated May 24, 2016 conducted for another referenced application; therefore, it was found adequate to support this NDA by the Drug Substance Reviewer. In addition, the two minor amendments recently submitted to the DMF were also reviewed and found acceptable by the Drug Substance Reviewer.

The drug product, clindamycin in 0.9% sodium chloride injection, is provided as a premixed, sterile, solution in GALAXY plastic containers and intended for intravenous administration. The drug product is supplied in three strengths, 300 mg/50 mL, 600 mg/50 mL, and 900 mg/50 mL, and contains clindamycin phosphate equivalent to 300 mg, 600 mg, and 900 mg of clindamycin, respectively. Excipients in the proposed formulation include sodium chloride (b) (4) and EDTA, (b) (4) In addition, sodium hydroxide and/or hydrochloric acid are added to adjust the pH (5.5 – 7.0). The currently proposed drug product is a new formulation of clindamycin injection, and includes a different tonicity adjuster as compared with the listed drug; i.e., 0.9% w/v sodium chloride versus 5% w/v dextrose used in the formulation of the listed drug. Due to similarities in the formulation, the Applicant has submitted a request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data for the proposed drug product. The biowaiver request was found acceptable by the Biopharmaceutics Reviewer.

The drug product specification includes tests and acceptance criteria for appearance, (clarity, color and particulate matter), pH, osmolality, particulate matter, assay by HPLC, impurities by HPLC, identification by retention time, identification by PDA, sterility, bacterial endotoxin and fill volume. The initially proposed acceptance criteria for pH and osmolality were revised during the NDA review at the FDA recommendations. In addition, several revisions were made to the acceptance criteria for impurities. Specifically, the initially proposed acceptance criteria for two specified impurities ((b) (4)), any unspecified impurity and total impurities were lowered and an acceptance criterion for total unspecified impurities was added. The drug product specification as revised was found acceptable by Drug Product Reviewers.

The manufacturing process for the proposed drug product, clindamycin in 0.9% sodium chloride injection, involves manufacturing (b) (4) the proposed process controls have been found adequate to mitigate potential risks to product quality by the Process Reviewer. In addition, information provided for the drug product from the product quality microbiology perspective (i.e., the sterilization validation, drug product specification and the container closure integrity) was found acceptable by the Product Quality Microbiology Reviewer.

The container closure system include Baxter's 50 mL single-port PL 2501 Plastic (GALAXY) Container Closure System, which has been previously used for a number of other FDA approved injectable products and was also found suitable for the currently proposed drug product. Based on the overall stability information provided in the initial NDA submission and subsequent amendments and taking into consideration the revised acceptance criteria for impurities, the 18-month expiration dating was granted for the drug product to be stored at room temperature.

The manufacturing facilities include (b) (4) (drug substance manufacturer) and Baxter Healthcare Corporation (drug product manufacturer). All facilities, including several testing facilities, were found acceptable in support of this NDA based on a review of the application and inspectional documents. Therefore, the overall recommendation of "Approve" was entered into Panorama on April 14, 2017.

Based on the above findings, the current overall recommendation from the Product Quality perspective is Approval (refer to the OPQ reviews entered into Panorama April 19, 2017).

4. Nonclinical Pharmacology/Toxicology

Dr. Tessie Alapatt was the Pharmacology/Toxicology Reviewer for this application. No nonclinical toxicology studies were conducted to support this NDA as the Applicant is relying on FDA's prior finding of the safety and effectiveness of the reference listed drug. The pharmacology/toxicology review focused on the assessment of acceptance criteria for impurities in the proposed drug product and the leachables from the container/closure system (GALAXY bag). The acceptance criteria for impurities, including two specified impurities, (b) (4), as revised by the Applicant during the NDA review, were found qualified based on the overall justification provided in the application. In addition, low levels of the leachable compound (b) (4) from the GALAXY bag identified for the proposed drug product, were also found qualified and of no concern. In conclusion, Dr. Alapatt recommended approval of this NDA. In addition, Dr. Alapatt recommended several minor revisions and modifications to Sections 8.1 and 8.2 of the proposed package insert (review dated April 14, 2017 in DARRTS).

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Dr. Kunyi Wu, stated that this application does not contain any new clinical pharmacology information; thus, this application is acceptable from a clinical pharmacology perspective. However, the Clinical Pharmacology Review Team has recommended several revisions in the package insert (review dated March 27, 2017 in DARRTS).

6. Clinical Microbiology

Jalal Sheikh, Ph.D., was the Clinical Microbiology Reviewer for this application.

No new clinical microbiology information was submitted in this application. The Microbiology Reviewer recommended approval of this application from the microbiology standpoint with several recommended minor changes in the microbiology section of the package insert to follow the current Division practice and recommendations of the FDA's draft guidance document: "Microbiological Data for Systemic Antibacterial Drug Products-Development, Analysis and Presentation" (review dated April 10, 2017 in DARRTS).

7. Clinical/Statistical – Efficacy

Maria Allende, MD, was the Clinical Reviewer, and Karen Higgins, Sc.D., was the Statistical Reviewer for this NDA.

Dr. Allende stated that this 505(b)(2) NDA, did not provide any new safety information that would alter the favorable risk/benefit assessment of clindamycin for the current labeled indications. Dr. Allende recommends this application for approval noting that the labeling revisions are pending (review dated March 15, 2017 in DARRTS).

As no clinical studies were conducted for this NDA, no statistical information was provided.

8. Safety

The Applicant of the current 505(b)(2) NDA is relying on the previous findings of safety for the listed drug, CLEOCIN PHOSPHATE IV Solution (clindamycin injection in 5% dextrose). The review of PubMed and Embase databases searches for additional safety data related to the use of the intravenous and oral clindamycin products yielded 57 references (in PubMed) and 85 (in Embase) in the last 5 years (up to 02/27/2017). Dr. Allende concluded that the reported adverse events are consistent with the adverse reactions listed in the current CLEOCIN labeling. In addition, since no additional adverse event information related to the use of clindamycin was identified, Dr. Allende concluded that safety-related changes in the current labeling are not warranted at this time (review dated March 15, 2017 in DARRTS).

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

10. Pediatrics

The drug product proposed via this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), does not apply to this application. No pediatric studies will be required as a condition of approval.

11. Other Relevant Regulatory Issues

No clinical studies/trials were conducted in support of this NDA. Therefore, no inspection request was sent to the Office of Scientific Investigations (OSI).

Based on the information in the electronic Orange Book, there are no unexpired patents and exclusivities for the listed drug, CLEOCIN PHOSPHATE IV Solution, marketed by Pfizer under NDA 50639.

12. Labeling

The proposed labeling and labels for the proposed drug product, Clindamycin in 0.9% Sodium Chloride Injection, were submitted in the NDA. No trade name was proposed.

Labeling revisions and recommendations were provided by all reviewers including DMEPA (review by Deborah Myers, RPh, MBA, dated April 3, 2017, in DARRTS). In addition, the Division of Pediatric and Maternal Health (DPMH) was consulted in the labeling review for this NDA and a number of revisions were recommended to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in the proposed package insert, to comply with the current PLLR requirements (review by Christos Mastroyannis, MD, dated April 5, 2017, in DARRTS). The labeling revisions recommended by FDA were incorporated in the final version of the package insert and in the 300 mg/50 mL container and carton labels.

(b) (4)

[redacted]

13. Recommendations/Risk Benefit Assessment

I concur with the assessments made by the review team and recommend the issuance of an Approval for this NDA.

Dorota M. Matecka -S