CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207131Orig1s000

SUMMARY REVIEW

Division Director Decisional Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Decisional Memo
NDA #	207131
Applicant Name	Celerity Pharmaceuticals, LLC
Date of Submission	October 16, 2014
PDUFA Goal Date	August 16, 2015
Established (USAN) Name	Cefazolin
Dosage Forms / Strength	2 g/100 mL cefazolin and 4% dextrose in a single-use GALAXY plastic container for injection
Proposed Indications	Preoperative prophylaxis
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Pharmacology Toxicology Review	Amy Ellis PhD
Chemistry Manufacturing and Controls Review	Chunchun Zhang PhD
Quality Biopharmaceutics Review	Kelly Kitchens, PhD
Cross-Discipline Team Leader Review	Balajee Shanmugam PhD
Medical Officer Review	Peter Kim MD MS
Statistical Review	Christopher Kadoorie PhD
Product Quality Microbiology Review	Vinayak Pawar, PhD
Clinical Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Kunyi Wu, Pharm D
Division of Medication Error Prevention and Analysis (DMEPA)	Sevan Kolejian, Pharm D
Office of Prescription Drug Promotion (OPDP)	Adam George, Pharm D

1.0 Introduction

NDA 207131, Cefazolin injection in GALAXY container was submitted by Celerity Pharmaceuticals, LLC on October 16, 2014. This is a frozen, premixed, iso-osmotic, sterile, non-pyrogenic solution of cefazolin packaged in GALAXY container (2 g (b) (4) 100 mL (b) (4) in each bag). Dextrose, USP is added to adjust the osmolality. The pH is adjusted with sodium bicarbonate (b) (4) to a range of 4.5 – 7.0. The proposed drug product is intended for intravenous use after thawing at room temperature or under refrigeration. This application is covered under 505(b)(2), relying on the Agency's previous findings of safety and effectiveness for the listed drug, Cefazolin Sodium USP and Dextrose USP in Duplex Container (NDA 50779, B. Braun Medical Inc.).

2.0 Background

The Applican (b) (4) the indication (b) (4) preoperative prophylaxis (b) (4) (b) (4)

The review team has completed their reviews of this application. For a detailed discussion of NDA 207131, please refer to discipline specific reviews and the Cross-Discipline Team Leader (CDTL) review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this application is Chunchun Zhang, PhD, and the Product Quality Microbiology reviewer is Vinayak Pawar, PhD.

For the drug substance, Cefazolin USP, reference was made to (b) (4) DMF (b) (4). The DMF was reviewed and found adequate on May 31, 2015. Cefazolin USP is a (b) (4)

(b) (4) in the pH range of 4 to 7). The specification for Cefazolin USP conforms to the current USP monograph; identification, water determination, assay, organic impurity, residual solvent, heavy metals are some of the quality attributes in the specification. Manufacturing process and control strategy provided in the DMF was found to be adequate. Stability data provided in the DMF supports a drug substance retest period of (b) (4).

Cefazolin injection, USP 2g/100 mL is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic solution in GALAXY plastic container (PL2040). The formulation, manufacturing process and equipment of the current proposed drug product (b) (4) The drug product contains 2g of Cefazolin USP, Dextrose USP (to adjust osmolality), sodium bicarbonate (to adjust pH) and water for injection.

Dr. Zhang notes that the drug product quality has been tested for the following final specifications: pH, identification, assay, impurities, osmolality, sterility, bacterial endotoxins particulate matter, and fill volume and all analytical methods have been adequately validated and the specification acceptance criteria justified adequately.

Overall, the stability data supports a 24-month expiration dating period at -20°C with a thawed label statement of "30 days under refrigeration (5°C/41°F) and 48 hours at room temperature (25°C/77°F)" when stored in GALAXY plastic container (PL 2040).

On July 29, 2015, the Office of Process and Facilities (OPF) issued an overall recommendation of "Acceptable" for this NDA.

Dr. Pawar recommends approval of the NDA from a product quality microbiology perspective.

At the time of filing the CMC review, Dr. Zhang did not recommend approval as the final recommendation from Dr. Pawar and from OPF was pending. In an addendum dated July 29, 2015, Dr. Zhang concludes that sufficient information has been provided to assure identity, strength, purity, and quality of the drug product and recommends approval of the NDA. I agree with her assessment.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this application is Amy Ellis, PhD. No new toxicology data were submitted in this NDA. Dr. Ellis recommends approval of the NDA from a pharmacology/toxicology perspective.

5.0 Biopharmaceutics

The Biopharmaceutics reviewer for this NDA is Kelly Kitchens, PhD. The Applicant requested a biowaiver per 21 CFR § 320.22 (b)(1), based on the following:

- The proposed drug product is an iso-osmotic, sterile solution intended solely for intravenous administration that has the same active ingredient in the same strength as the reference product.
- The dosage form, route of administration and dosing regimen for the proposed drug are the same as the reference product.

Dr. Kitchens has granted the biowaiver request and recommends approval of the NDA.

6.0 Clinical Microbiology

Kerian Grande Roche, PhD, is the clinical microbiology reviewer for this application. No new clinical microbiology information was submitted in this application. As this product only has an indication for preoperative prophylaxis, the Microbiology subsection (12.4) was updated (b) (4) Labeling recommendations have been incorporated in the Microbiology subsection of the package insert.

7.0 Clinical Pharmacology

Kunyi Wu, PharmD, is the clinical pharmacology reviewer for this application. Dr. Wu notes that no new clinical pharmacology information was submitted in the NDA. Dr. Wu's recommendations for labeling have been incorporated. Dr. Wu notes that the NDA is acceptable from a clinical pharmacology perspective.

8.0 Clinical Efficacy/Safety

Peter Kim, MD MS, is the clinical reviewer for this application. No new efficacy or safety data were submitted in this NDA. Dr. Kim performed a review of the literature from 2011-2014 and no new adverse events were identified. A search of the FDA Adverse Events Reporting System (FAERS) from 2011-2014 also did not identify any new safety signals.

As noted in Dr. Kim's addendum, the indication for this product is for preoperative prophylaxis (b) (4) The B. Braun label (NDA 50779) states the following in the Dosage and Administration Section:

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

- 1 to 2 gram IV administered 1/2 hour to 1 hour prior to the start of surgery.
- For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV during surgery (administration modified depending on the duration of the operative procedure).
- 500 mg to 1 gram IV every 6 to 8 hours for 24 hours postoperatively.

As this product can only be administered as a 2 gram dose and not as 500 mg or 1 gram, the indication (b) (4) preoperative prophylaxis. Labeling also includes a Limitation of Use statement in the Indications and Usage section which states that an alternative cefazolin product should be used when lengthy surgical procedures require supplemental doses and when postoperative dosing is required. The Dosage and Administration section includes a statement that the product should only be used in patients needing the entire 2 gram and not a fraction.

Dr. Kim recommends approval of the NDA. I agree with his assessment.

Christopher Kadoorie, PhD, is the statistics reviewer for this NDA. Dr. Kadoorie notes that no new clinical data were submitted and that the proposed labeling changes are acceptable. Dr. Kadoorie agrees with the clinical reviewer's assessment that the NDA be approved.

9.0 Labeling

Labeling recommendations from all disciplines were incorporated in the final labeling. Sevan Kolejian, PharmD, from the Division of Medication Error Prevention and Analysis performed a labeling review and her recommendations for labeling revisions have been incorporated. Labeling recommendations from Adam George, PharmD, from the Office of Prescription Drug Promotion have also been incorporated in labeling. (b) (4) . Hence, the Pediatric Use section (Section 8.4) has been revised to state that safety and effectiveness for the pediatric population has not been established.

21 CFR 201.24, labeling for systemic antibacterial drug products states that in the "Precautions" section, under the "Information for Patients" subsection, the labeling must state:

Patients should be counseled that antibacterial drugs including (insert name of antibacterial drug product) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When (insert name of antibacterial drug product) is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by (insert name of antibacterial drug product) or other antibacterial drugs in the future.

As this product is only administered as a single dose preoperatively, this language was not included in the Patient Counseling Information section (17) of the labeling.

10.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. None of these criteria apply for this application therefore, PREA requirements are not applicable to this NDA.

11.0 Other Regulatory Issues

This application was not presented to the Anti-Infective Drugs Advisory Committee (AIDAC), as there were no issues requiring input from the AIDAC.

12.0 Recommended Regulatory Action

I agree with the assessment made by the review team that NDA 207131, Cefazolin for injection in GALAXY container be approved, relying on the Agency's previous finding of safety and effectiveness of NDA 50779 (Cefazolin Sodium USP and Dextrose USP in Duplex Container). I recommend approval of this NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
08/07/2015