sNDA Summary Review

NDA #/Supplement #	207131/S-010
Applicant	Baxter HealthCare Corporation
Date of Submission	July 31, 2023
PDUFA Goal Date	May 31, 2024
Proprietary Name / Established (USAN) names	Cefazolin in Dextrose Injection*
Dosage forms/Strength	Injectable Solution, 3g/150ml
Proposed Indication(s)	Perioperative prophylaxis in adult patients weighing ≥ 120 kg
Regulatory Action	Approval

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

1. Background

NDA 207131 for Cefazolin in Dextrose Injection (previously referred to as Cefazolin Injection) supplied as 2g cefazolin in 100 mL of a premixed frozen iso-osmotic solution in a single-use Galaxy plastic container was approved on August 7, 2015. A 1g/50 mL presentation was approved on February 1, 2021.

On July 31, 2023, Baxter HealthCare Corporation (Applicant) submitted this efficacy supplement for a 3g/150 mL presentation for the indication of perioperative prophylaxis in adult patients weighing greater than or equal to 120 kilograms. This is a 505 (b)(2) application which relies on the Listed Drug (LD), Cefazolin for Injection and Dextrose Injection, (NDA 050779). In support of this efficacy supplement the Applicant conducted a pharmacokinetic (PK) study of cefazolin to compare the PK exposure from a single dose of Cefazolin injection, 2g/100 mL in healthy subjects weighing less than 120 kg with that of Cefazolin injection, 3g/150 mL in subjects weighing greater than or equal to 120 kg.

2. Review of Current Submission

Regulatory:

The Applicant submitted an efficacy supplement on July 31, 2023, for a 3g/150 mL presentation for the indication of perioperative prophylaxis in adult patients weighing greater than or equal to 120 kilograms. The proposed 3g/150 mL Cefazolin in Dextrose Injection was subject to the Pediatric Research Equity Act (PREA) requirements because the proposed 3-gram dose represents a new dosing regimen for cefazolin for the perioperative prophylaxis indication. The Applicant has submitted an Agreed initial Pediatric Study Plan (iPSP) wherein the Applicant requested a partial waiver for pediatric patients weighing less than 120 kg because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a

substantial number of patients in this group. The request for a partial waiver was reviewed and agreed upon by the Pediatric Review Committee (PeRC) and the Division of Anti-Infectives.

The user fee goal date for this efficacy supplement is May 31, 2024.

Chemistry Manufacturing and Controls (CMC):

Cefazolin in Dextrose Injection is currently commercially available for adults in a single-dose solution containing either 1g Cefazolin per 50 mL or 2g Cefazolin per 100 mL in a Galaxy container. The proposed 3g/150 mL presentation is made in the same fashion from the same active pharmaceutical ingredient (API) and packaged in the GALAXY container closure system with the same materials in contact with the solution as the approved presentations, and only differs in the fill volume and bag size. The new presentation has met the specification.

The submission is acceptable from an OPQ perspective. Three registration batches were placed on stability for evaluation, and all passed all required tests. The Office of Pharmaceutical Manufacturing Assessment (OPMA) has approved the facility for the new presentation. Quality microbiology has found the supplement adequate, and the submission is recommended for approval on the basis of sterility assurance. Biopharmaceutics has indicated that no action is indicated. Refer to the CMC review uploaded in PANORAMA for details (CMC Rev 2 - NDA-207131-SUPPL-10.docx on May 15, 2024).

Clinical Pharmacology:

The Clinical Pharmacology review of this submission focused on the aforementioned open label PK study in healthy adult subjects that compared cefazolin exposure following a 3g cefazolin single intravenous (IV) dose in subjects weighing ≥ 120 kg (n=12) with exposure following a 2g cefazolin single IV dose in subjects weighing < 120 kg (n=12). The study findings demonstrated that the cefazolin exposure after 3g dose in subjects weighing ≥ 120 kg and after 2g dose in subjects weighing < 120 kg was similar. Overall, the clinical pharmacology information submitted under this supplement is adequate and the Applicant's proposed labeling revisions are acceptable from a clinical pharmacology perspective. (Please see the Clinical Pharmacology review in DARRTS dated April 26, 2024, for additional details.)

Clinical:

The review of the PK study in healthy adult subjects, and published literature in adult and pediatric patients on the safety of cefazolin 3-gram injection in perioperative prophylaxis have not identified any new safety signals for cefazolin for injection.

Labeling:

Prescribing Information (PI)

The labeling revisions from the recently approved supplement for Supplement 009 of this NDA including information regarding the addition of pediatric patients aged 10 to 17 years old to the approved indication for perioperative prophylaxis throughout the PI, and addition of prothrombin activity in the Warnings and Precautions (5.5), and Adverse Reactions, Cephalosporin-class Adverse Reactions (6.3) were incorporated into the PI submitted under this efficacy supplement. Refer to the Supplement 009 approved PI in DARRTS dated 2/1/2024 for additional details.
Additional significant labeling changes to the Supplement 10 PI submitted on July 31, 2023, are summarized in the table below.

Summary of Significant Labeling Changes made to the Prescribing Information submitted on July 31, 2023		
Section/Subsection	**Applicant's Proposed Labeling**	**FDA Recommended Labeling**
HIGHLIGHTS (HL) OF PRESCRIBING INFORMATION	HL and Rest of PI Established name of "(b) (4)" was changed to "Cefazolin in Dextrose Injection" in the HL and the rest of the PI. RECENT MAJOR CHANGES Dosage and Administration, Important Administration Information (2.1) Dosage and Administration, Dosage for Treatment Infections (2.2) Dosage and Administration, Dosage for Perioperative Prophylaxis (2.3) DOSAGE AND ADMINISTRATION Indication: Perioperative prophylaxis Dose	Accepted the new established name: "Cefazolin in Dextrose Injection." This was based on the rationale provided by OPQ that "Cefazolin in Dextrose Injection" is a USP monograph title, which is permissible after 5/1/2022. For additional details refer to CMC Rev 2 - NDA-207131-SUPPL-10.docx on 5/15/2024. Updated the Recent Major Changes (RMC) date from "X/2024" to 5/2024." Editorial revisions were also made to align the subsection headings in the RMC with the FPI headings (b) (4) and for 2.2 "the" was added). Dose was revised as follows to remove medication error prone symbols: Dose

	<120 kg: 1 gram to 2 grams ≥120 kg: 3 grams Frequency: ½ to 1 hour prior to start of surgery DOSAGE FORMS AND STRENGTHS	Less than 120 kg: 1 gram to 2 grams Greater than or equal to 120 kg: 3 grams Added the new strength,3 grams in 150 mL after 1 gram in 50 mL and 2 grams in 100 mL.
FULL PRESCRIBING INFORMATION		
2. DOSAGE AND ADMINISTRATION Subsection 2.3 Dosage for Perioperative Prophylaxis	Added revisions to Table 3: Recommended Dosage for Perioperative Prophylaxis in Adults with CLcr of 55 mL/min or Greater as follows: Added Body Weight: Less than 120 kg Greater than or equal to 120 kg Revised 1g and 2 g for less than 120 kg dose and added 3 g dose for greater than or equal to 120 kg.	Accepted with minor edits and formatting changes.
11 DESCRIPTION	Addition of the 3-gram strength and description of cefazolin sodium, including an equivalency statement to indicate the name and strength of both the active ingredient (Salt) and the active moiety as follows: “3g Cefazolin, USP equivalent to 3.15 g Cefazolin Sodium, USP per 150 mL Galaxy container (PL 2040 Plastic)”.	Accepted with minor changes. For additional details, refer to CMC Rev 2 - NDA-207131-SUPPL-10.docx on 5/15/2024
12 CLINICAL PHARMACOLOGY	Added introductory text	Accepted with minor edits and formatting changes. For

Subsection 12.3 Pharmacokinetics	to new table 8 added as follows: "Plasma pharmacokinetic parameters of cefazolin in healthy (b) (4) greater than 120 kg (N=12) following a single 30- minute IV infusion of 3 grams of Cefazolin in Dextrose Injection are summarized in Table 8. Table 8 provided a summary of the mean (standard deviation plasma pharmacokinetic parameters of cefazolin in healthy volunteers ≥ 120 kg	additional details, refer to the Clinical Pharmacology review in DARRTS dated April 26, 2024.
16 HOW SUPPLIED/STORAGE AND HANDLING	Labeling text proposed as introductory statement as follows: (b) (4) (b) (4)	Revised the introductory statement to add "sterile" and "non-pyrogenic" and removed (b) (4) to read as "Cefazolin in Dextrose Injection is supplied as a premixed, frozen, iso-osmotic, sterile, nonpyrogenic solution in single-dose Galaxy plastic containers as follows:" Removed (b) (4) For all three strengths, added the concentration per mL (20

	[redacted] (b) (4) and NDC Number: NDC 0338-0096-06. Applicant proposed the statement: "Store in a freezer capable of maintaining a temperature of -20°C (-4°F) or below [redacted] (b) (4) Handle frozen product containers with care. Product containers may be fragile in the frozen state."	mg/mL) to the product description column and a new column for the Number of Containers/Carton. Removed [redacted] (b) (4) and added the following statement that recommends special handling and storage conditions as per 21 CFR 201.57 (c)(17): "Thaw frozen container at room temperature 20°C to 25°C (68°F to 77°F) or under refrigeration 2°C to 8°C (36°F to 46°F). Do not force thaw by immersion in water baths or by microwave irradiation. The thawed solution is stable for 30 days under refrigeration (5°C/41°F) or 48 hours at 25°C/77°F. Do not refreeze *[see Dosage and Administration (2.5)]*.

Carton and Container Labeling Changes

The revisions applied to the carton and container labeling are based on the recommendations of the Division of Medication Error Prevention and Analysis 1 (DMEPA-1). Please see the DMEPA review for further details (signed into DARRTS on February 20,2024 and March 12, 2024).

3. Regulatory Action

This efficacy New Drug Application NDA 207131/S-010) for Cefazolin in Dextrose Injection 3 grams in150 mL will receive an approval action.

Reviewers:

Clinical: Alma Davidson, MD

Clinical Pharmacology Reviewer: Meng Wang, PhD
Clinical Pharmacology Team Leader: Abhay Joshi, PhD
CMC Reviewer: Jason Deck, PhD
CMC Team Leader: Ramesh Gopalaswamy, PhD
Associate Director for Labeling: Abimbola O, Adebowale, MS, PhD
Deputy Division Director: Dmitri Iarikov, MD, PhD

Signatures: *{See appended electronic signature page}*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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