OFFICE OF CLINICAL PHARMACOLOGY REVIEW

Application Type:	Application Number:	IND Type:
☐ IND ☒ NDA ☐ BLA ☐ Consult Other: Click or tap here to enter text.	207131/S-010 Submission Number (SDN): 133, 134, and 145 Submission Date: 7/31/2023, 09/12/2023, and 03/15/2024	☒Commercial ☐Research ☐EIND

Generic name: Cefazolin in Dextrose Injection	Sponsor: Baxter HealthCare Corporation
Therapeutic Area: Anti-Infective Route of Administration: Intravenous Injectable	Indication: • Perioperative prophylaxis in adult patients weighing ≥ 120 kg

Proposed Dosage:
Add a new dosing regimen of 3 g/150 ml for the indication of perioperative prophylaxis in adult patients weighing greater than or equal to 120 kilograms.

Submission Content:

☐ 30 Day Safety	☐ Meeting Package		☐ Protocol Review
☐ IR Response review	☐ PSP	☐ SPA	☐ BPCA Related
☒ Other: NDA supplement			

OCP Review Division: Division of Infectious Disease Pharmacology (DIDP)

Primary Reviewer: Meng Wang, Ph.D.	Secondary Reviewer: Abhay Joshi, Ph.D.

Development Stage: Post Approval

Description of Submission:
The Applicant submitted this NDA efficacy supplement to propose a new dosing regimen of 3 g/150 ml for perioperative prophylaxis in adult patients weighing greater than or equal to 120 kg

Executive Summary:
Clinical pharmacology information submitted under the efficacy supplement (NDA207131/S-10) and the Applicant proposed labeling revisions are acceptable from a clinical pharmacology perspective.

Regulatory History/Background:
Cefazolin is a semi-synthetic, first-generation cephalosporin antibacterial drug that has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections including Gram-positive bacteria (Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes), and Gram-negative bacteria (Escherichia coli and Proteus mirabilis).

The Applicant submitted this efficacy supplement on July 31, 2023, for Cefazolin in Dextrose Injection 3 g/150 mL. This supplemental application proposes to add a new drug product presentation, 3 g/150 ml for the indication of perioperative prophylaxis in adult patients weighing greater than or equal to 120 kg. This is a 505 (b)(2) application which relies on the Listed Drug (LD), Cefazolin for Injection and Dextrose Injection, B. Braun Medical Inc. (NDA 050779) for the Agency's prior findings of safety and efficacy. In this application, the Applicant conducted a pharmacokinetic (PK) study of cefazolin to compare the PK exposure from a single dose of Cefazolin injection, 2 g/100 mL in subjects weighing less than 120 kg with that of Cefazolin injection, 3 g/150 mL in subjects weighing greater than or equal to 120 kg.

Review Issue/Topic: Evaluation of the proposed dosing regimen of 3 g for perioperative prophylaxis in adult patients weighing greater than or equal to120 kg

Background Related to Review Issue/Topic:

In the submission, the Applicant proposed revisions to the currently recommended cefazolin dosage for the perioperative prophylaxis indication in adults are noted in red text within the Table 1 below.

Table 1: Recommended Dosage for Perioperative Prophylaxis in Adults with CLcr of 55 mL/min or Greater

Body weight (kg)	Dose administered ½ hour to 1 hour prior to the start of surgery	Additional dose during lengthy operative procedures (e.g., 2 hours or more)	Dose for 24 hours postoperatively
Less than 120 kg	1 gram to 2 grams	500 mg to 1 g	500 mg to 1 g every 6 hours to 8 hours
Greater than or equal to 120 kg	3 grams		

In support of the proposed revisions, the Applicant has submitted following as supporting evidence:

- Clinical practice guidelines for antimicrobial prophylaxis in surgery[1]
- Surgical infection prevention guidelines writers workgroup; antimicrobial prophylaxis for surgery: an advisory statement from the national surgical infection prevention project (2004)[2]
- Literature reported data to support 3 g used in overweight patients[3,4]
- A comparative pharmacokinetics (PK) study (BXU578918) in healthy subjects

Reviewer's Assessment:

The aforementioned clinical guidelines were reviewed from a clinical pharmacology perspective. The clinical practice guidelines for antimicrobial prophylaxis in surgery noted that "*Considering the low cost and favorable safety profile of cefazolin, increasing the dose to 2 g for patients weighing more than 80 kg and to 3 g for those weighing over 120 kg can easily be justified*." However, the guideline does not provide any specific supporting information for this dosage adjustment. In the surgical infection prevention guidelines writers workgroup, it is mentioned that "*In a study of obese patients undergoing gastroplasty, blood and tissues levels of cefazolin were consistently below the minimum inhibitory concentration for gram-positive and -negative organisms in patients who received a 1-g*

[1] Bratzler DW, et al. American Society of Health-System Pharmacists; Infectious Disease Society of America; Surgical Infection Society; Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013 Feb 1;70(3):195-283.

[2] Bratzler DW, Houck PM. Surgical Infection Prevention Guideline Writers Workgroup. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Am J Surg. 2005 Apr;189(4):395-404.

[3] Swank ML, et al. Increased 3-gram cefazolin dosing for cesarean delivery prophylaxis in obese women. Am J Obstet Gynecol. 2015 Sep;213(3):415.

[4] Smyth RD, et al. Clinical pharmacokinetics and safety of high doses of ceforanide (BL-S786R) and cefazolin. Antimicrob Agents Chemother. 1979 Nov;16(5):615-21.

dose before surgery [48]. Those patients receiving 2 g cefazolin had a lower incidence of SSI than those receiving a 1-g dose", however, it does not explicitly mention the use of a 3 g dose in the prophylaxis regimen. Therefore, the two guidelines mentioned above do not offer detailed clinical pharmacology related information, data, or evidence to support the selection of 3 g dose in patients with body weight ≥120 kg.

The submitted literature in support of the use of 3 g in overweight patients was also reviewed from a clinical pharmacology perspective. The literature findings suggest that increasing the dose to 3 g for obese patients may be necessary, and that 3 g of cefazolin in patients is generally safe. Specifically, Swank ML et al. reported that following the administration of 2 g of cefazolin, subjects weighing <120 kg exhibited tissue concentrations higher than the subjects weighing > 120 kg. The Applicant also cited Smyth et al. that investigated the clinical pharmacokinetics and safety of high doses of cefazolin. This study reported that all side effects were mild and transient with doses up to 4 g twice daily for 25 days. However, the provided literature do not contain a study directly comparing the efficacy or exposure of a single 2 g dose in patients weighing less than 120 kg to a 3 g dose in patients weighing greater than or equal to 120 kg. Also, the literature does not include bioanalytical method validation to support the pharmacokinetic (PK) data for the 3 g dose of cefazolin. Therefore, the clinical pharmacology review of this submission focused on the cefazolin PK findings from Study BXU578918 that compared cefazolin PK in subjects with < 120 kg and ≥ 120 kg weight who received a single dose of 2 g and 3 g cefazolin, respectively.

From a clinical pharmacology perspective, we agree with the Applicant's proposal of 3 g starting dose for perioperative prophylaxis in adults with body weight ≥120 kg and creatinine clearance (CL_{Cr}) ≥ 55 mL/min. The Applicant's proposal is acceptable based on the findings from a pharmacokinetic (PK) study (Study BXU578918, summarized below) and the following safety related information:

- Study BXU578918 demonstrated that the cefazolin exposure after 3 g dose in subjects weighing ≥ 120 kg and after 2 g dose in subjects weighing < 120 kg was similar. See the next section for additional details for Study BXU578918.
- The most recent approved label for NDA 207131 (dated 02/01/2024) and the listed drug's label (ANCEF®, NDA 050461) note that in rare instance, doses up to 12 grams of cefazoline per day have been used.
- The Applicant conducted a retrospective study to evaluate the safety of preoperative 3 g vs. 2 g IV cefazolin administered for the prevention of surgical site infections (SSIs) in adults weighing ≥ 120 kg. The study analyzed a real-world database comprised of electronic health records (n=2090) from 95 hospitals located throughout the US. The study concluded that the occurrence of neurotoxicity and superficial phlebitis in the patient population was very low.

Regarding the submitted/cited literature in support of the safety, we defer to the clinical review team.

Review Issue/Topic: Review of Individual clinical pharmacology related study

Background Related to Review Issue/Topic:

Study BXU578918

This was a comparative PK study designed as a phase 1, open label, single dose, two arms study of 2 different doses of cefazolin injection, 3 g/150 mL (Group A: Subjects with ≥ 120 kg weight) or cefazolin injection 2 g/100 mL (Group B: Subjects with < 120 kg weight), administered intravenously over 30

minutes in healthy male and nonpregnant female subjects under fasting condition. In total, 24 subjects were enrolled, and all subjects completed the study. Demographic information is summarized in Table 1. For PK assessments, blood samples were collected to measure the cefazolin concentration at 15 minutes prior to start of infusion and at 2, 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, and 480 minutes after end of infusion.

Table 1. Demographic Characteristics Summary

Category /Statistics	Group A (N = 12)	Group B (N = 12)	Overall (N = 24)
Age (Years)			
n	12	12	24
Mean	37.8	40.6	39.2
SD	10.08	11.39	10.62
Median	37.0	38.5	37.5
Minimum	21	22	21
Maximum	50	54	54
Sex, n(%)			
Male	9 (75.0)	7 (58.3)	16 (66.7)
Female	3 (25.0)	5 (41.7)	8 (33.3)
Race, n(%)			
Asian	0	1 (8.3)	1 (4.2)
Black or African American	11 (91.7)	8 (66.7)	19 (79.2)
White	1 (8.3)	3 (25.0)	4 (16.7)
Ethnicity, n(%)			
Hispanic or Latino	1 (8.3)	2 (16.7)	3 (12.5)
Not Hispanic or Latino	11 (91.7)	9 (75.0)	20 (83.3)
Unknown	0	1 (8.3)	1 (4.2)
Height(cm)			
n	12	12	24
Mean	177.4	171.0	174.2
SD	9.05	11.36	10.57
Median	180.0	172.5	176.0
Minimum	159	152	152
Maximum	194	190	194
Weight(kg)			
n	12	12	24
Mean	133.32	81.94	107.63
SD	11.746	14.335	29.203
Median	127.80	79.40	112.50
Minimum	121.3	61.2	61.2
Maximum	152.6	103.7	152.6
BMI (kg/m^2)			
n	12	12	24
Mean	42.69	28.08	35.39
SD	6.400	4.470	9.210
Median	41.55	28.15	35.65
Minimum	35.4	21.6	21.6
Maximum	60.4	35.9	60.4

Group A = Dose of 3 g/150 mL cefazolin injection; Group B = Dose of 2 g/100 mL cefazolin injection.
Abbreviation: BMI = Body mass index, N = number of subjects in Safety Analysis Set in specific dosage group or overall; n = number of subjects in specific category in Safety Analysis Set in specific dosage group or overall; % = (n/N)×100; SD = standard deviation.
Height, weight, and BMI at Screening visit are considered.

Source: NDA 207131 Module 5.3.3.1 BXU567633 Clinical Study Report Full Body 2022 December 07. Table 10

The PK findings are summarized in Table 2. The study results suggest that plasma concentrations exhibited low intrasubject variability, which is 13.9% and 13.7% for Cmax and AUC_{0-t}, respectively. For comparing the cefazolin PK between both the groups, the geometric mean ratio (GMR) [90% confidence interval (CI)] for Cmax and AUC_{0-t} were derived, and the findings are summarized in Table 2. The findings suggest that the Cmax estimates are comparable between both the groups, as it falls within the criteria routinely used to evaluate bioequivalence (BE), i.e., 90% CI range of 80%-125%.

However, the upper bound for 90% CI of AUC ratio is slightly exceeds the upper boundary of acceptance criteria of 125%. (see Table 3)

Table 2 Summary Statistics of Cefazolin Plasma Pharmacokinetics Parameter by Dosage Group (Group A:3 g/150 mL; Group B: 2 g/150 mL)

Parameter (unit)	Statistics	Group A 3g/150 mL (n=12)	Group B 2g/150 mL (n=12)
C_{max} (µg/mL)	Arithmetic Mean (CV%)	223 (11.7)	208 (15.7)
AUC_{0-t} (h*µg/mL)	Arithmetic Mean (CV%)	539 (11.2)	466 (16.1)
AUC_{0-inf} (h*µg/mL)	Arithmetic Mean (CV%)	585 (13.1)	495 (15.8)
T_{max} (h)	Median (min, max)	0.55 (0.54, 1.26)	0.54 (0.54, 0.58)
$T_{1/2}$ (h)	Arithmetic Mean (CV%)	2.29 (12.4)	2.04 (10.9)
CL(L/h)	Arithmetic Mean (CV%)	5.20 (12.8)	4.12 (13.1)
Vz (L)	Arithmetic Mean (CV%)	17.0 (9.1)	12.1 (16.5)

Source: NDA 207131 Module 5.3.3.1 Supplemental Report to BXU567633 2023 August 25

Table 4. Statistical Analysis of Plasma Pharmacokinetics Parameters of Cefazoline to Assess Similarity of PK profiles (Group A:3 g/150 mL; Group B: 2 g/150 mL)

	Geometric Mean (90% CI)						
PK Parameter (unit)	**n**	**Group A**	**n**	**Group B**	**% Ratio (Group A/Group B)**	**90% CI of Ratio**	**Intra-Subject CV%**
C_{max} (µg/mL)	12	221.445 (206.81, 237.12)	12	205.425 (191.85, 219.96)	107.798	97.86, 118.74	13.9
AUC_{0-t} (min×µg/mL)	12	32169.302 (30168.20, 34303.13)	12	27696.816 (25973.93, 29533.98)	116.148	106.06, 127.19	13.0

Abbreviations: CV = coefficient of variation, CI = confidence interval, n = number of subjects with non-missing and non-excluded value, PK = Pharmacokinetic.

Source: NDA 207131 Module 5.3.3.1 BXU567633 Clinical Study Report Full Body 2022 December 07. Table 12

Reviewer's Assessment:

The observed higher AUC level (~16%) for 3 g group is acceptable based on the following available safety information:

- In the most recent approved label for NDA 207131 (dated 02/01/2024), it mentioned that in rare instance, does up to 12 grams of cefazoline per day have been used.
- For the study BXU578918 in the current submission, the Applicant stated that in the 3 g group, only one subject reported treatment emergent adverse events (TEAE) which was mild in severity.
- To support the safety of administering Cefazolin 3 g in patients with body weight over 120 kg, the Applicant has analyzed study sample which was drawn from a real-world database comprised of electronic health records from 95 hospitals located throughout the US. All patients who underwent surgery between [redacted] (b) (6) and who met all of the inclusion criteria and none of the exclusion criteria were included in the study; post-operative outcome data was available up to 01 July 2021. Neurotoxicity and superficial phlebitis within 12 hours of cefazolin administration is used as endpoint for the safety assessment. The study concluded that the occurrence of neurotoxicity and superficial phlebitis in the patient population was very low.

We defer to clinical review team for the final decision with regards to safety.

Overall, the use of 3 g for the patients with bodyweight ≥120 kg is acceptable from a clinical pharmacology perspective.

Review Issue/Topic: Evaluation of bioanalytical method validation

Background Related to Review Issue/Topic:

Table 4. A summary of bioanalytical method and its validation

Method Type	LC-MS/MS	
Validation Report#	1255-R12466, Addendum Report No. 1255-R12466AI	
Studies Analyzed	BXU567633	
Biological Matrix	Plasma	
Anticoagulant	K_2 EDTA	
Calibration curve	2.00 µg/mL (LLOQ), 6.00 µg/mL, 240 µg/mL, 600 µg/mL, and 1000 µg/mL (Dilution QC) for Cefazolin	
Analyte of Interest	Cefazolin	
Internal Standard	Cefazolin-$^{13}C_2$,^{15}N for Cefazolin	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)[a]	≤13% for LLOQ; ≤9.2% for the other QCs	Yes
Intra-run precision (for all QC concentrations)[a]	≤14.4%	Yes
Inter-run accuracy (for all QC concentrations)[a]	-0.7% to ≤6.0%	Yes
Inter-run precision (for all QC concentrations)[a]	2.7% to ≤7.7%	Yes
Selectivity	No response ≥5% Internal Standard	Yes
Short-term or bench-top temperature stability	21.0 hours at Room Temperature	Yes
Freeze-Thaw stability	5 freeze (-20 °C)/thaw (room temperature) cycles 5 freeze (-70 °C)/thaw (room temperature) cycles	Yes
Long-term storage	-20 °C for 101 days and -70 °C for 101 days, 165 days, and 448 days.	Yes
Incurred Sample Reanalysis[b]	-16.7%-19.5% (42 plasma study samples)	Yes

[a]All accuracy and precision values are presented as the combined ranges from validation and performance reports across studies
[b]At least 10% of samples were reanalyzed for incurred sample reanalysis

Reviewer's Assessment:

The bioanalytical method validation is acceptable.

Additionally, the bioanalytical study report (#1255-R12825) supports the cefazolin concentration determination in K_2EDTA human plasma samples originating from Study BXU567633. The human plasma analytical runs QC samples met the acceptance criteria. No repeat analysis was needed to be

performed because all the calibration runs were successful. Overall, the bioanalytical results are acceptable from a clinical pharmacology perspective.

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/s/

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