CLINICAL STUDY PROTOCOL

IND NUMBER: 106043

A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery

PROTOCOL NUMBER: HC-G-H-1601

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Version of Protocol:	Final 2.0
Date of Protocol:	Original Protocol, Version 1.0: 15 Sep 2016 Amendment 1, Version 2.0: 24 Mar 2017

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery
Protocol Number	HC-G-H-1601
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Protocol Date	24 March 2017

Protocol accepted and approved by:

Corporate Vice President, Medical Affairs

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Signature

28 March 2017
Date

Protocol Approval – Sponsor Signatory

Study Title	A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery
Protocol Number	HC-G-H-1601
Protocol Version	2.0
Protocol Date	24 March 2017

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3/28/17.
Date

Protocol Approval – Sponsor Signatory

Study Title	A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery
Protocol Number	HC-G-H-1601
Protocol Version	2.0
Protocol Date	24 March 2017

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24 Mar 2017
Date

Protocol Approval – Sponsor Signatory

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Protocol Number	HC-G-H-1601
Protocol Version	2.0
Protocol Date	24 March 2017

Protocol accepted and approved by:

Corporate Vice President, Regulatory Affairs

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Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the final protocol version 2.0, dated 24 March 2017, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol. I will not implement protocol changes without B. Braun Medical Inc. approval and institutional review board approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from B. Braun Medical Inc.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	HC-G-H-1601
Title:	A Phase 4, Open-Label, Single-Dose, Parallel-Group Study to Evaluate the Safety of 1 g of Cefazolin in Pediatric Subjects With a Weight of at Least 25 kg but Less Than 60 kg Scheduled for Surgery and the Safety of 2 g of Cefazolin in Pediatric Subjects With a Weight of at Least 60 kg Scheduled for Surgery
Sponsor:	B. Braun Medical Inc. 901 Marcon Boulevard Allentown, PA 18109-9341 USA
Study Phase:	Phase 4
Study Sites:	Approximately 5 sites (to a maximum of 15 sites) in the United States
Indication:	Perioperative infection prophylaxis
Rationale:	B. Braun Medical Inc. conducted a human pharmacokinetic (PK) and safety study to obtain marketing approval for pediatric use of cefazolin 1 g or 2 g strength single-dose in the United States with identical indications of those already approved for the 1 g or 2 g strength single-dose in adults (Study HC-G-H-1202) (B. Braun Medical Inc. 2014). The study evaluated 12 pediatric surgical subjects aged 10 to 12 years. Based on study results and the revised population PK model for cefazolin (Trang et al 2014), the recommended weight-based dosing for pediatric surgical subjects is as follows: • 1-g cefazolin for pediatric surgical subjects weighing ≥25 to <60 kg, and • 2-g cefazolin for pediatric surgical subjects weighing ≥60 to ≤85 kg. The proposed study (HC-G-H-1601) is a postmarketing requirement established by the US Food and Drug Administration as part of the Pediatric Research Equity Act to evaluate the safety of cefazolin in children aged 10 to 17 years (inclusive) receiving weight-based 1 g or 2 g of cefazolin intravenously over 30 minutes delivered via the DUPLEX® container for surgical prophylaxis. Pharmacokinetic blood samples will be collected in a subset of subjects to determine the cefazolin plasma concentrations. Cefazolin plasma concentrations will be used to refine the population PK model.

The details of the refined population PK model analysis will be contained in a separate report. The study is designed to follow clinical practice and overall experience with cefazolin administration.

Objectives:

Primary objective:

To evaluate the safety of a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

Secondary objective:

To determine the cefazolin plasma concentrations following a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

Subject Population:

Inclusion Criteria:

1. The subject is between the ages of 10 and 17 years (inclusive) at the time of giving informed consent.
2. The subject is scheduled for surgery that will last less than 3 hours.
3. The subject and the subject's legally authorized representative voluntarily agree that the subject will participate in this study. In accordance with applicable laws, regulations, and institutional review board requirements, the subject signs or orally agrees to an age-appropriate assent and the subject's legally authorized representative signs both an institutional review board-approved informed consent form and Health Insurance Portability and Accountability Act authorization prior to the performance of any screening procedures.
4. For subjects who agree to participate in the PK subgroup additional consent will be obtained.
5. The subject weighs (on Day 1) ≥25 kg but <60 kg for inclusion in 1 g dose group.
6. The subject weighs (on Day 1) ≥60 kg for inclusion in 2 g dose group.
7. The subject has been scheduled for any type of surgery requiring single-dose perioperative cefazolin prophylaxis.

Exclusion Criteria

1. Female subjects who are pregnant or lactating/breastfeeding.
2. Female subjects of childbearing potential who are sexually active and who are not willing to use an effective method of birth control during the study period, eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy.
3. The subject has impaired renal function based on the revised Schwartz formula (Schwartz et al 2009) using actual body height, ie, estimated glomerular filtration rate $\leq$80 mL/minutes/1.73 m^2 (performed at Screening if test results are not available within 3 months prior to the planned surgery).
4. The subject has a known allergy or hypersensitivity to β-lactam/cephalosporin antibiotics, penicillins, corn products, or dextrose-containing products or solutions, or any of the other ingredients of Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP in DUPLEX.
5. The subject has abnormal vital signs or an abnormal electrocardiograph (ECG) considered by the investigator to be clinically significant.
6. The subject has a result of any laboratory test (or repeat test, if done), obtained as standard of care, that is outside the normal limit of the site's laboratory reference range AND is considered by the investigator to be clinically significant.
7. The subject has had a recent (within 7 days prior to the planned surgery) administration of cefazolin.
8. The subject has had administration of any medication (eg, prescription, herbal, over-the-counter medication[s] or dietary supplements) known to interact with cefazolin within 5 days prior to the study drug administration. Concomitant use of probenecid is prohibited
9. The subject has a known history of human immunodeficiency virus, hepatitis B, or hepatitis C infection.
10. The subject has a history of alcohol or drug abuse.

11. The subject has received any other investigational drug/device within 30 days prior to the study drug administration.
12. The subject has a recent history or medical condition(s), which in the opinion of the investigator, would interfere with the evaluation of the study drug.
13. The subject has any planned medical intervention or personal event that might interfere with ability to comply with the study requirements.
14. The subject has any condition that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.
15. The subject is unable or unwilling to adhere to the study-specified procedures and restrictions.
16. The subject has a history of or is currently smoking or using nicotine-containing substances or electronic cigarettes as determined by medical history or subject's verbal report.
17. The subject or his/her legally authorized representative (LAR) is an employee of the investigator or study center with direct involvement in this study or other studies under the direction of that investigator or study center, or is a family member of an employee of the investigator or study center.

Study Design:

This is a Phase 4, open-label, single-dose, parallel-group, multicenter, safety study of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

Approximately 110 subjects will be enrolled and assigned to 1 of the 2 dose groups in a 1:1 ratio (55 subjects in each group). Subjects with a weight of at least 25 kg but less than 60 kg will receive a single dose of 1-g cefazolin. Subjects with a weight of at least 60 kg will receive a single dose of 2-g cefazolin. Dose groups will not be balanced by age or gender. Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

During the Screening Period (up to 30 days before the study drug administration), all subjects will have screening and baseline examinations performed to ensure their eligibility for

	the study. Study drug will be administrated on Day 1 (day of surgery) over 30 minutes as an infusion starting 0.5 to 1 hour before surgery begins and following institutional guidelines. Planned surgical procedures may be performed in an outpatient or inpatient setting and are expected to last no longer than 3 hours. If the surgery is unexpectedly extended beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines. Safety will be assessed by monitoring adverse events (AEs), physical examination, vital signs, ECGs, and clinical laboratory tests. During the Follow-up Period, a follow-up visit will be performed on Day 8 (±1 day) for safety assessments. In a subset of approximately 40 subjects, 4 PK samples will be obtained to determine the cefazolin plasma concentrations in this population. Pharmacokinetic samples will be obtained at 0.5 to 1.0 hours, 2.0 hours (±15 minutes), 3.0 hours (±15 minutes), and 4.0 hours (±15 minutes) after the start of the study drug infusion. A minimum of 10 of the 40 subjects are planned to be 10 to 13 years old. If the surgery is unexpectedly extended beyond the 3-hour limit and an additional dose of study drug will be administered, best efforts will be made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug. Pharmacokinetic sample collection will not continue after the administration of an additional dose of study drug. Additional subjects may be enrolled if necessary to ensure availability of complete PK data from at least 40 subjects. Subject completion is defined as completion of the follow-up visit or the time of the subject's last data collection. In the cases of an additional dose of study drug, subjects from whom a 3-hour PK sample is obtained prior to administration of the additional dose are considered PK completers.
Estimated Study Duration:	The study consists of a Screening Period of up to 30 days, a Treatment Period on Day 1 (day of surgery), and a Follow-up Period including a visit on Day 8 (±1 day). The maximal study duration for an individual subject will be 39 days.
Safety Assessments:	Safety will be determined by monitoring AEs, physical examinations, vital signs, ECGs, and clinical laboratory tests.

Study drug, Dosage, and Route of Administration:

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single-use, packaged combination of Cefazolin Sodium USP (lyophilized) and iso-osmotic diluent (ie, Dextrose Injection USP) in the DUPLEX container. The DUPLEX container is a flexible dual-chamber container. Cefazolin Sodium USP (active ingredient) is supplied in the drug chamber as a lyophilized form equivalent to 1 g or 2 g of cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.

The following drug supplies will be used in the study:

Product[1]	Strength	Diluent	Route
Cefazolin Sodium USP	1 g	4% Dextrose Injection USP, 50 mL	Intravenous
Cefazolin Sodium USP	2 g	3% Dextrose Injection USP, 50 mL	Intravenous

Abbreviation: USP, United States Pharmacopeia.

[1] Supplied as a lyophilized form for injection in the DUPLEX container.

Sample Size:

Approximately 110 subjects (males and females) will be enrolled in the study.

A subset of approximately 40 subjects (males and females across both dose groups) will be enrolled in the PK subgroup. A minimum of 10 of the 40 PK subjects are planned to be in the 10 to 13 years old age bracket.

Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study including 40 subjects with complete PK data.

Statistical Methods:

Descriptive statistics will be presented for all safety parameters. Continuous variables will be summarized by treatment group using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

No inferential statistical analysis will be performed.

Cefazolin plasma concentrations will be summarized with descriptive statistics.

Date of Protocol:

Version 2.0, 24 March 2017

List of Abbreviations

Abbreviation	Definition
AE	adverse event
CDROM	compact disk read-only memory
CFR	Code of Federal Regulations
ECG	electrocardiograph
eCRF	electronic case report form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IV	intravenous
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over the counter
PD	pharmacodynamic
PK	pharmacokinetic(s)
SAE	serious adverse event
SD	standard deviation
SID	subject identification
SSI(s)	surgical site infection(s)
USP	United States Pharmacopeia
w/v	weight to volume ratio

1 Introduction

1.1 Background

Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP is a sterile, nonpyrogenic, single-use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent (ie, Dextrose Injection USP) in the DUPLEX® sterile container.

Cefazolin Sodium USP and Dextrose Hydrous USP are supplied as a lyophilized form equivalent to either 1 g or 2 g of cefazolin (ie, contains approximately 2 g dextrose [4.0% weight to volume ratio (w/v)] and 1.5 g dextrose [3.0% w/v] for the 1 g and 2 g dosages, respectively).

Microbiology

Cefazolin is an antibacterial agent that in in vitro testing has been shown to act by inhibition of bacterial cell wall synthesis.

Cefazolin has demonstrated activity against most strains of the following microorganisms, both in vitro and in clinical infections:

Gram-Positive Bacteria

- *Staphylococcus aureus* (*S aureus*)
- *Staphylococcus epidermidis*
- *Streptococcus pyogenes* (*S pyogenes*) and *Streptococcus agalactiae* (*S agalactiae*)
- *Streptococcus pneumonia (S pneumoniae*)

Methicillin-resistant staphylococci are uniformly resistant to cefazolin, as are many strains of enterococci resistant to cefazolin.

Gram-Negative Bacteria

- *Escherichia coli* (*E coli*)
- *Proteus mirabilis* (*P mirabilis*)

Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter* spp, *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp, and *Pseudomonas* spp are resistant to cefazolin.

Indications and Usage

Cefazolin for Injection USP and Dextrose Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria:

Respiratory Tract Infections

- Respiratory tract infections due to *S pneumoniae*, *S aureus,* and *S pyogenes*

Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available.

Urinary Tract Infections

- Urinary tract infections due to *E coli* and *P mirabilis*

Skin and Skin Structure Infections

- Skin and skin structure infections due to *S aureus*, *S pyogenes*, and *S agalactiae*

Biliary Tract Infections

- Biliary infections due to *E coli*, various strains of streptococci, *P mirabilis*, and *S aureus*

Bone and Joint Infections

- Bone and joint infections due to *S aureus*

Genital Infections

- Genital infections due to *E coli* and *P mirabilis*

Septicemia

- Septicemia due to *S pneumoniae*, *S aureus*, *P mirabilis*, and *E coli*

Endocarditis

- Endocarditis due to *S aureus* and *S pyogenes*

Perioperative Prophylaxis

The prophylactic administration of cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (eg, vaginal hysterectomy and cholecystectomy in high-risk patients such as those older than 70 years and those with acute cholecystitis, obstructive jaundice, or common bile duct stones).

The perioperative use of cefazolin may also be effective in surgical patients for whom infection at the surgical site would present a serious risk (eg, during open-heart surgery or prosthetic arthroplasty).

Pharmacodynamics in Humans

It is commonly accepted that β-lactam antibiotics exhibit time-dependent killing of bacteria. Thus, the percentage of time that drug concentrations remain above the minimum inhibitory concentration for the bacterial pathogen is the relevant pharmacokinetic (PK)/pharmacodynamic (PD) index for cefazolin (Leggett et al 1989).

Pharmacokinetics in Humans

Absorption

Cefazolin is only available as an intravenous (IV) formulation. Thus, no human bioavailability data are available for other routes of administration.

Distribution

Studies have shown that after IV administration of cefazolin to healthy volunteers, mean serum concentrations peaked at approximately 185 µg/mL and were approximately 4 µg/mL at 8 hours for a 1-g dose.

Bile concentrations in patients without obstructive biliary disease could reach or exceed serum concentrations by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin were considerably lower than serum concentrations (<1.0 µg/mL).

In synovial fluid, the cefazolin concentration became similar to that reached in serum at approximately 4 hours after drug administration.

Studies of cord blood showed prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Metabolism

Cefazolin is not a substrate, inducer, or inhibitor of hepatic cytochrome P450 isoenzymes. No significant amounts of metabolite have been observed in human plasma.

Excretion

Cefazolin is excreted unchanged in the urine. In the first 6 hours, approximately 60% of the drug is excreted in the urine, and this increases to 70% to 80% within 24 hours.

The mean serum half-life for cefazolin is approximately 1.8 hours after IV administration.

Adult Pharmacokinetic Studies

In a study (using healthy volunteers) of constant IV infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg for the next 2 hours (approximately 100 mg), cefazolin produced a steady serum concentration at the third hour of approximately 28 µg/mL.

Plasma PK parameters of cefazolin in healthy volunteers (n=12) after a single 15-minute IV infusion of 2 g of Cefazolin for Injection USP and Dextrose USP (the formulation being evaluated in the current proposed study) are summarized in Table 1-1.

Table 1-1 Plasma Pharmacokinetic Parameters of Single-Dose Cefazolin of 2 g as a 15-Minute Intravenous Infusion in Healthy Volunteers

	N	C_{max} (μg/mL)	T_{max}[1] (h)	AUC_{0-inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Mean (SD)	12	280.9 (45.9)	0.25 (0.25-0.33)	509.9 (89.3)	2.01 (0.28)	4.03 (0.68)	11.50 (1.53)

Abbreviations: AUC_{0-inf}, area under the plasma concentration-time curve extrapolated to infinity; CL, total clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent plasma terminal elimination half-life; T_{max}, time to maximum plasma concentration; V_z, volume of distribution.

[1] T_{max} reported as median (range).

Studies in patients hospitalized with infections indicated that cefazolin produces mean peak serum concentrations approximately equivalent to those seen in healthy volunteers.

Pediatric Pharmacokinetic Studies

Relatively few pediatric PK studies have been conducted for cefazolin.

Koshida et al examined the PK of cefazolin in 6 pediatric subjects aged 3 to 12 years receiving 25 mg/kg of cefazolin after cardiac catheterization. Ten blood samples for cefazolin analysis (both free- and total-drug) were obtained in each child beginning at the end of the cefazolin infusion; the final PK sample was drawn 280 minutes (4.7 hours) after the start of the infusion. The mean half-life in the 6 subjects was 108 minutes (approximately 1.8 hours), similar to the mean half-life in adults. The mean volume of distribution was 0.133 L/kg, which is also similar to that observed in adults. The serum protein binding of cefazolin ranged from 45.0% to 82.3% (Koshida et al 1987).

In a follow-up study of 5 obese children aged 1 to 9 years, Koshida et al determined that the PK of cefazolin was unaffected by obesity (children were an average of 63% above ideal body weight). Cefazolin half-life and volume of distribution were 100 minutes and 0.135 L/kg, respectively (Koshida et al 1989).

Nahata et al studied the PK of cefazolin in 9 children (aged 0.8 to 10 years) undergoing gastrointestinal surgeries. Subjects received a single dose of cefazolin, 15 to 26 mg/kg intravenously over 2 to 3 minutes, at the time of induction of anesthesia. The PK parameter estimates were found to be similar to those observed in adults; the mean terminal elimination half-life for cefazolin was 1.68 hours. The authors also found that tissue concentrations of

cefazolin were maintained above its minimum inhibitory concentration for common susceptible pathogens at the time of surgical wound closure (approximately 2 hours after first incision) (Nahata et al 1991).

Haessler et al examined the PK of cefazolin in 19 infants less than 10 kg undergoing cardiac surgery with cardiopulmonary bypass. Subjects received 40 mg/kg of cefazolin intravenously at induction of anesthesia and 35 mg/kg every hour over the subsequent 48 hours. Prior to cardiopulmonary bypass, cefazolin half-life was somewhat shorter (mean of 0.9 hours) and volume of distribution was somewhat larger (mean of 0.191 L/kg) compared with that observed in older children from previous studies. The authors found that the use of cardiopulmonary bypass had a significant effect on cefazolin PK. However, the authors concluded that serum cefazolin concentrations were consistent with those required for satisfactory efficacy (Haessler et al 2003).

A recent study (Study HC-G-H-1202) examined the PK of cefazolin in 12 pediatric surgical subjects (aged 10 to 12 years). Subjects received a single dose of cefazolin, 1 g or 2 g over 30 minutes, for surgical prophylaxis. The PK of cefazolin in pediatric surgical subjects differed from that previously recorded in healthy adults and it was evident that the weight cutoff for cefazolin dose (1 g for those weighing ≥25 to <50 kg and 2 g for those weighing ≥50 to ≤85 kg) did not appropriately compensate for the effect of body size on the PK of cefazolin. A revised PK model estimated that the total clearance of cefazolin is 33.5% lower in pediatric surgical subjects than in healthy adults after correcting for differences in body size and mean creatinine clearance. A weight cutoff of 60 kg was suggested as an appropriate threshold for a 1-g cefazolin dose (Schmitz et al 2015).

Cies et al evaluated body mass index (BMI) and antimicrobial dose as risk factors for surgical site infections (SSIs) in a retrospective case-control study of 105 case and 212 control pediatric patients between 2 and 19 years of age. The authors found that being underweight and undergoing an operation lasting >2 hours created significant risks for SSI. Children weighing ≥70 kg receiving a standard 1-g dose of cefazolin had a greater risk of methicillin-sensitive *Staphylococcus aureus* (MSSA) SSIs than children weighing <70 kg who received an appropriate weight-based dose of this antibiotic (Cies et al 2012).

Smits et al examined the cefazolin binding to human serum albumin (HSA) and its effect on dosing in 40 neonates undergoing surgery. Intravenous cefazolin (50 mg/kg) was

administered prior to a surgical procedure, and the total and unbound cefazolin plasma concentrations (mg/L) were determined at 0.5, 2, 4, and 8 hours after cefazolin administration. The investigators found the median unbound cefazolin fraction in neonates is higher than in adults and depends partly on albuminaemia, total cefazolin concentration, indirect bilirubinaemia and postmenstrual age. The authors suggested integration of cefazolin protein binding in future PK/PD research is warranted in order to optimize neonatal cefazolin dosing (Smits et al 2012).

Himebauch et al performed prospective study that included 17 children (aged 13.4 to 15.4 years) with adolescent idiopathic scoliosis undergoing posterior spinal fusion. The purpose of this study was to determine the PK and skeletal muscle disposition of prophylactic cefazolin using serial plasma and microdialysis samples during the surgical procedure. The amount of time that the concentration of unbound cefazolin exceeded the minimal inhibitory concentration for bacterial growth for selected SSI pathogens was calculated. The results suggest that the dosing strategy of cefazolin used in the study (one or two doses of 30 mg/kg cefazolin) is likely to be adequate for intraoperative SSI prophylaxis against MSSA but might not prevent infections from some common Gram-negative pathogens (Himebauch et al 2016).

Safety and Efficacy

Pediatrics

Schmitz et al published data of a PK and safety study that used Cefazolin for Injection USP and Dextrose Injection USP, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent in the DUPLEX® sterile container, at a dose of 1g or 2g in pediatric patients. The investigators observed one serious adverse event (SAE), hypotension, which was possibly related to the cefazolin treatment. The subject underwent inhalation induction with oral intubation, receiving propofol and morphine for the surgical excision of a left branchial cleft cyst. Eight minutes after anesthetic induction, a 30 minute IV infusion of a 2-g dose of cefazolin as antibiotic prophylaxis commenced. Eighteen minutes after the start of cefazolin administration, the patient intraoperatively experienced moderate hypotension. No other significant clinical assessments were recorded. The subject was treated with three 20-mg doses of phenylephrine and a 500-mL IV bolus of Ringer's lactate. The patient's systolic blood pressure returned to normal while in the recovery area and no further evidence

of hypotension was observed. None of the other adverse events (AEs) were assessed as related to cefazolin and there were no discontinuations from the study because of AEs (Schmitz et al 2015).

Yilmaz et al report the case of a 12-year-old boy who received cefazolin and gentamycin (unknown dosage, route, and frequency) for suspected septic arthritis. The patient developed drug hypersensitivity reaction with drug rash, eosinophilia and systemic symptoms (DRESS) including severe interstitial nephritis 3 weeks after the start of the treatment. He was treated successfully by discontinuing the two drugs, hemodialysis and 3-day IV and oral combination therapy with prednisolone (Yilmaz et al 2016).

Surgical Prophylaxis

There are no reports of adequate and well-controlled randomized prospective studies of surgical prophylaxis for pediatric patients in the literature. One prospective study in burn patients showed no benefit from cefazolin prophylaxis (Rodgers et al 1997).
Two retrospective studies (1 cardiac [Maher et al 2002], 1 orthopedic [Nahata et al 1985]) lacked non-cefazolin control arms; in one, the use of fixed doses of cefazolin was associated with an overdose risk (Nahata et al 1985). One survey (Lee et al 1995) and 3 PK/PD studies (Koshida et al 1987; Nahata et al 1991; Haessler et al 2003) evaluated cefazolin intravenously in surgical prophylaxis. Dosing varied widely, but 25 mg/kg repeated every 8 hours for up to 48 hours represents a consensus position. The results of a retrospective analysis comparing the efficacy of two antimicrobial prophylaxis (AMP) protocols with cefazolin in preventing surgical site infection in adolescent idiopathic scoliosis suggest that two doses of AMP are as effective as continued antimicrobial use until drain removal and cefazolin appears to be effective and safe for prophylaxis (Kamath et al 2016).

In a single-center retrospective study, Cies et al evaluated the risk factors and the impact of weight-based regimen of perioperative antibiotics on the risk for surgical site infection in pediatric subjects between 2 and 19 years of age who underwent clean orthopedic surgical procedures and received at least 1 dose of a perioperative antibiotic (cefazolin, vancomycin, or clindamycin). Being underweight and undergoing an operation that lasted more than 2 hours created significant risks for surgical site infection. For children weighing at least 70 kg, receiving a standard dose of cefazolin (1 g) had a greater risk of surgical site infection caused by methicillin-sensitive *S aureus* (Cies et al 2012).

Adverse Events

Cefazolin is well tolerated and there is little mention of AEs in the published literature. One study noted no AEs in a series of only 5 subjects (Ross et al 1977) and another noted no AEs in 52 subjects (Nahata et al 1985). Two other reports noted eosinophilia (Khan 1973; Ross et al 1977), and hepatic dysfunction and rash were also noted (Khan 1973).

Controlled studies on adult healthy volunteers receiving 1 g 4 times a day for 10 days that monitored complete blood count, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and urinalysis indicated no clinically significant changes attributed to cefazolin.

Safety data in the recent study (Study HC-G-H-1202) have suggested that a dose of 1 g of cefazolin infused intravenously over a period of 30 minutes for infection prophylaxis during surgical procedures appeared to be well tolerated. A single SAE of hypotension that was deemed possibly related to study drug was reported in 1 of the 4 children who received a 2-g dose of cefazolin (B. Braun Medical Inc. 2014). It has not been established if the event of hypotension was due to anesthesia induction or cefazolin. (Schmitz et al 2015).

The B. Braun Medical Inc. 1 g cefazolin finished product currently approved by FDA has been marketed since 2001 with a total unit volume of 76,255,382 through November 2016. The B. Braun Medical Inc. 2 g cefazolin finished product was approved in adult populations on 13 January 2012 and first sales to the US market were on 13 February 2012 with a total unit volume of 22,688,762 through November 2016. Only 39 AEs have been reported with the use of cefazolin. Of these 39 AEs, 11 were serious/unexpected (8 of which were from literature and not confirmed to be the B. Braun Medical Inc. product). The remaining 28 AEs included 9 non-serious/expected and 19 serious/expected events. For a full description of the AEs please refer to the investigator's brochure (B. Braun Medical Inc. 2017).

1.2 Rationale for the Clinical Study

Currently, cefazolin is a standard of care for perioperative infection prophylaxis in pediatric patients. Older children and adolescents may benefit from the availability of a fixed-dose system for the prophylactic administration of cefazolin, a commonly prescribed antibiotic used for surgical prophylaxis in a wide variety of surgical procedures.

Ancef® (cefazolin for injection) has been approved for pediatric patients older than 1 month (Ancef 2004). Total daily dosage for pediatric patients may be increased to 100 mg per kg of body weight for severe infections. It is also recommended for perioperative prophylactic use to prevent postoperative infection.

B. Braun Medical Inc. intends to conduct a safety study and obtain marketing approval for pediatric use of cefazolin of 1 g and 2 g strength single-dose in the United States. The proposed study (HC-G-H-1601) is a postmarketing requirement established by the FDA as part of the Pediatric Research Equity Act to evaluate the safety of cefazolin in children aged 10 to 17 years (inclusive) receiving weight-based 1 g or 2 g of cefazolin intravenously over 30 minutes delivered via the DUPLEX drug delivery system for surgical prophylaxis.

In addition, PK blood samples will be collected in a subset of subjects to determine the cefazolin plasma concentrations following a single 30-minute infusion in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery. Cefazolin plasma concentrations will be used to refine the population PK model. The details of the refined population PK model analysis will be contained in a separate report.

1.3 Risk-Benefit Assessment

Cefazolin is a first generation cephalosporin antibiotic with a well-established and favorable safety profile that has been in use for almost 40 years (originally approved in 1973). It is a standard of care for perioperative prophylaxis today and widely recommended for prophylaxis for a variety of surgical procedures for the prevention of infections by gram-positive bacteria. Cefazolin has been shown to be active against some gram-negative bacteria, such as *E. coli* and *P. mirabilis*. Subjects will be recruited from among those already scheduled to have a surgical procedure in which cefazolin will have already been chosen as the prophylactic antibiotic.

The safety monitoring practices employed in this study are adequate to protect the subjects' safety and detect all expected treatment-emergent AEs.

The volume of blood planned for collection from each subject (Table 1-2) over the course of the entire study (Screening to Follow-up, but not including repeat or additional tests ordered by the investigator) follows the standard of local laboratory practices and presents no undue risk to the subjects.

Table 1-2 Blood Volume

Sample Type	Total Blood Volume (Planned)
Clinical Laboratory	32 mL (8 mL × 4 collections)
Pharmacokinetic	16 mL (4 mL × 4 collections)
Combined Clinical and Pharmacokinetic	48 mL

The available information suggests that the present clinical study has an acceptable risk-benefit ratio.

2 Study Objectives

The primary objective of this study is to evaluate the safety of a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

The secondary objective of this study is to determine the cefazolin plasma concentrations following a single 30-minute infusion of a weight-based dose of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery.

3 Investigational Plan

3.1 Study Design

This is a Phase 4, open-label, single-dose, parallel-group, multicenter, safety study of cefazolin (1 g or 2 g) in pediatric subjects between 10 and 17 years of age (inclusive) scheduled for surgery. This study will be conducted at approximately 5 study sites (to a maximum of 15 sites) in the United States.

Approximately 110 subjects will be enrolled and assigned to 1 of the 2 dose groups in a 1:1 ratio (55 subjects in each group). Subjects with a weight of at least 25 kg but less than 60 kg will receive a single dose of 1-g cefazolin. Subjects with a weight of at least 60 kg will receive a single dose of 2-g cefazolin. Dose groups will not be balanced by age or gender. Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

The study consists of a Screening Period of up to 30 days, a Treatment Period on Day 1 (day of surgery), and a Follow-up Period including a visit on Day 8 (±1 day). The maximal study duration for an individual subject will be 39 days.

During the Screening Period (up to 30 days before the study drug administration), all subjects will have screening and baseline examinations performed to ensure their eligibility for the study. Study drug will be administrated on Day 1 (day of surgery) over 30 minutes as an infusion starting 0.5 to 1 hour before surgery begins and following institutional guidelines. Planned surgical procedures may be performed in an outpatient or inpatient setting and are expected to last no longer than 3 hours. If the surgery is extended unexpectedly beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines (Section 5.1). Safety will be assessed by monitoring AEs, physical examination, vital signs, ECGs, and clinical laboratory tests. During the Follow-up Period, a follow-up visit will be performed on Day 8 (±1 day) for safety assessments.

In addition, 4 PK samples will be obtained in a subset of approximately 40 subjects to determine the cefazolin plasma concentrations in this population. Pharmacokinetic samples will be obtained at 0.5 to 1.0 hours, 2.0 hours (± 15 minutes), 3.0 hours (± 15 minutes), and 4.0 hours (± 15 minutes) after the start of the study drug infusion. A minimum of ten of the 40 PK subjects are planned to be in the 10 to 13 year old age bracket. If the surgery is

unexpectedly extended beyond the 3-hour limit and an additional dose of study drug will be administered best efforts will be made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug. Pharmacokinetic sample collection will not continue after the administration of an additional dose of study drug.

Subject completion is defined as completion of the follow-up visit or the time of the subject's last data collection. In the cases of an additional dose of study drug, subjects from whom a 3-hour PK sample is obtained prior to administration of the additional dose are considered PK completers.

Please refer to Table 3-1 for detailed assessments and schedule.

3.1.1 Rationale of Study Design

The design of this study follows current clinical practice and overall experience with cefazolin administration for perioperative infection prophylaxis. Cefazolin is widely used for perioperative infection prophylaxis in adult and pediatric patients.

Based on the PK results of cefazolin in 12 pediatric surgical subjects aged 10 to 12 years from Study HC-G-H-1202 (B. Braun Medical Inc. 2014), and the revised population PK model for cefazolin (Trang et al 2014), the upper weight limit of 59 kg is set for the 1-g dose. Subjects weighing greater than or equal to 60 kg will receive the 2-g dose.

As required by the FDA, the proposed study will enroll approximately 110 subjects (55 subjects per dose group) aged 10 to 17 years to evaluate the safety of a weight-based single dose of cefazolin (1 g or 2 g) (Section 7.2).

Sparse PK samples from a subset of approximately 40 subjects will be obtained after the start of the study drug infusion to determine the cefazolin plasma concentrations. Plasma concentration data will be used to further refine the population PK model. The details of the refined population PK model analysis will be contained in a separate report.

Table 3-1 Schedule of Events

Study Phase	**Screening Period**	**Treatment Period (Day of Surgery)**							**Follow-up Period**
Procedure	**Screening[1]**	**Pre-surgery**	**Surgery**					**Post-surgery[2]**	**Safety Follow-up Visit[3]**
Study Day	**Up to 30 Days Before Study Drug Administration**	**1**						**1 or 2**	**8 (±1)**
Time point after start of infusion			**15 min (±5 min)**	**0.5 h – 1.0 h**	**2.0 h (±15 min)**	**3.0 h (±15 min)**	**4.0 h (±15 min)**		
Informed consent for study participation	X								
Informed consent for pharmacokinetic (PK) participation	X								
Inclusion/exclusion criteria	X								
Subject identification number assignment	X								
Demographics	X								
Height (without shoes)	X								
Weight[4]	X	X							
Medical history	X								
Medication history	X								
Updated medical history for eligibility		X							
Physical examination[5]	X	X						X	X

Study Phase	**Screening Period**	**Treatment Period (Day of Surgery)**							**Follow-up Period**
Procedure	**Screening[1]**	**Pre-surgery.**	**Surgery**					**Post-surgery[2]**	**Safety Follow-up Visit[3]**
Study Day	**Up to 30 Days Before Study Drug Administration**	**1**						**1 or 2**	**8 (±1)**
Vital signs[6, 7]	X	X[7]	X	X		X		X	X
Electrocardiograph (ECG)[6]	X							X	
Clinical Laboratory tests (blood)[8]	X[9]	X						X	X
Pregnancy test[10]	X	X							
Study drug infusion site assessment			X	X		X		X	X
Pharmacokinetic blood collection[11]				X	X	X	X		
Concomitant medications	Continuous								
Adverse event monitoring	Continuous								
Study drug administration[12]		X							

[1] If Screening visit occurs on Day 1 (day of surgery), all Screening visit assessments must be properly completed.

[2] Postsurgery assessments will be performed at 24 hours after surgery or discharge from the study site, whichever comes first.

[3] Safety Follow-up visit will be performed for subjects who complete the study or terminate prematurely after receiving study drug, whenever possible.

[4] Weight will be measured with indoor clothing and without shoes.

[5] Details of physical examination are outlined in Section 6.2.2. The complete physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems). A brief physical examination will be performed both before and after dosing on Day 1 and at the Safety Follow-up visit.

[6] Vital signs (including blood pressure [systolic and diastolic], pulse, body temperature, and respiratory rate) and ECGs should be taken with subjects in supine position after resting for 5 minutes. Details of vital sign measurements are outlined in Section 6.2.3. Details of ECGs are outlined in Section 6.2.4. Vital signs and ECG obtained at Screening will be considered as Baseline.

[7] Predose vital sign measurements should be obtained within approximately 30 minutes before the start of study drug administration.

[8] Clinical laboratory tests will include hematology and clinical chemistry. Details of laboratory tests are outlined in Section 6.4. Laboratory tests except for screening procedures will be performed by the central laboratory.

[9] Screening laboratory tests should be performed within 30 days of Day 1 and can be the same tests as those assessed for surgical clearance. Screening laboratory tests will be performed at local laboratories.

[10] Urine pregnancy tests will be performed for all females of childbearing potential at Screening and be repeated on Day 1. If positive, pregnancy will be confirmed with serum test. If pregnancy is confirmed, the subject will not be enrolled or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

[11] Pharmacokinetic blood samples will be obtained at the designated time points after the start of the study drug infusion. NOTE: The catheter that is used for study drug infusion and the arm it is inserted in cannot be used for collection of the PK samples. Pharmacokinetic samples must be taken from the opposite arm of the study drug infusion.

[12] Study drug will be administered over 30 minutes as an infusion starting 0.5 to 1 hour before surgery begins and following institutional guidelines. The start time of the study drug infusion and the start time of the anesthesia induction will be recorded in the eCRF. Subjects with a weight of at least 25 kg but less than 60 kg will receive 1-g cefazolin. Subjects with a weight of at least 60 kg will receive 2-g cefazolin. If the surgery is extended unexpectedly beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines (Section 5.1).

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 110 subjects will be enrolled at approximately 5 study sites (up to 15) in the United States. Subjects will be assigned to study drug administration only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is between the ages of 10 and 17 years (inclusive) at the time of giving informed consent.
2. The subject is scheduled for surgery that will last less than 3 hours.
3. The subject and the subject's legally authorized representative (LAR) voluntarily agree that the subject will participate in this study. In accordance with applicable laws, regulations and institutional review board requirements, the subject signs or orally agrees to an age-appropriate assent and the LAR signs both an institutional review board (IRB)-approved informed consent form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to the performance of any screening procedures.
4. For subjects who agree to participate in the PK subgroup additional consent will be obtained.
5. The subject weighs (on Day 1) ≥25 kg but <60 kg for inclusion in 1 g dose group.
6. The subject weighs (on Day 1) ≥60 kg for inclusion in 2 g dose group.
7. The subject has been scheduled for any type of surgery requiring single-dose perioperative cefazolin prophylaxis.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Female subjects who are pregnant or lactating/breastfeeding.
2. Female subjects of childbearing potential who are sexually active and who are not willing to use an effective method of birth control during the study period eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy.
3. The subject has impaired renal function based on the revised Schwartz formula (Schwartz et al 2009) using actual body height, ie, estimated glomerular filtration rate ≤80 mL/minute/1.73 m^2 (performed at Screening if test results are not available within 3 months prior to the planned surgery); the Schwarz formula is the following:

$$\text{Glomerular filtration rate} = \frac{0.41 \times \text{height (cm)}}{\text{serum creatinine (mg/dL)}}$$

4. The subject has a known allergy or hypersensitivity to β-lactam/cephalosporin antibiotics, penicillins, corn products, or dextrose-containing products or solutions, or any of the other ingredients of Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX.
5. The subject has abnormal vital signs or an abnormal ECG considered by the investigator to be clinically significant.
6. The subject has a result of any laboratory test (or repeat test, if done), obtained as standard of care, that is outside the normal limit of the site's laboratory reference range **AND** is considered by the investigator to be clinically significant.
7. The subject has had a recent (within 7 days prior to the planned surgery) administration of cefazolin.
8. The subject has had administration of any medication (eg, prescription, herbal, over-the-counter [OTC] medication[s] or dietary supplements) known to interact with cefazolin within 5 days prior to the study drug administration. Concomitant use of probenecid is prohibited.

9. The subject has a known history of human immunodeficiency virus, hepatitis B, or hepatitis C infection.
10. The subject has a history of alcohol or drug abuse.
11. The subject has received any other investigational drug/device within 30 days prior to the study drug administration.
12. The subject has a recent history or medical condition(s), which in the opinion of the investigator, would interfere with the evaluation of the study drug.
13. The subject has any planned medical intervention or personal event that might interfere with ability to comply with the study requirements.
14. The subject has any condition that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.
15. The subject is unable or unwilling to adhere to the study-specified procedures and restrictions.
16. The subject has a history of or is currently smoking or using nicotine-containing substances or electronic cigarettes as determined by medical history or subject's verbal report.
17. The subject or his/her LAR is an employee of the investigator or the study center with direct involvement in this or other studies under the direction of that investigator or study center, or is a family member of an employee of the investigator or study center.

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the completion of the follow-up visit on Day 8 (±1 day). For those subjects who withdraw prematurely, subject completion is defined as the time of the subject's last data collection.

4.2.1 Reasons for Withdrawal/Discontinuation

Any subject, or his or her LAR on behalf of the subject, may withdraw from the study at any time and for any reason without prejudice to the subject's future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. If the subject is unreachable by at least 2 telephone calls, a registered letter, at the minimum,

should be sent to the subject requesting that he or she contacts the investigator. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria
2. Noncompliance with the protocol
3. A serious or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study
4. Lost to follow-up
5. Pregnancy
6. Request to withdraw informed consent or HIPAA authorization by subject or LAR
7. Any other reason warranting withdrawal at the discretion of the investigator with approval of B. Braun Medical Inc.

Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed up to satisfactory resolution (Section 6.2.1.6). Any subject or his or her LAR on behalf of the subject may withdraw the consent at any time. The investigator will also withdraw a subject if B. Braun Medical Inc. terminates the study.

4.2.2 Handling of Withdrawals

Subjects, or LAR on behalf of the subject, are free to withdraw from the study or study drug at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study prematurely, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page in the electronic case report form (eCRF). Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all safety assessments scheduled for the safety follow-up visit on Day 8. Subjects who are unreachable for final assessments will be contacted by the study site in an attempt to have them comply with the protocol (Section 4.2.1).

It is vital to obtain follow-up data on any subject withdrawn because of a serious or intolerable AE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

Female subjects who are known to be pregnant should not be enrolled in the study. All female subjects will have a pregnancy test at Screening and on Day 1 (presurgery). If a pregnant subject is administered study drug in error, the subject will be followed though completion or termination of the pregnancy. Please refer to Section 6.3 for specified reporting and follow-up processes.

4.2.3 Replacements

Subjects who discontinue the study will not be replaced in this study. Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

5 Study Treatments

All screened subjects are assigned unique subject identification (SID) numbers. The SID numbers are 7-digit numbers that identify subjects from time of Screening. Enrolled subjects who withdraw from the study will retain their SID numbers.

5.1 Study Drug Administration

A peripheral venous catheter will be placed for all subjects before the start of the study drug administration for the IV infusion of the cefazolin and dextrose solution. Subjects with a weight of at least 25 kg but less than 60 kg will receive 1-g cefazolin. Subjects with a weight of at least 60 kg will receive 2-g cefazolin. After reconstitution, the solution will be administered over 30 minutes through an infusion line by using an infusion pump on Day 1 (day of surgery) for surgery prophylaxis. The study drug administration will begin 0.5 to 1 hour prior to the start of surgery and following institution guidelines.

If the surgery is unexpectedly extended beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines.

For subjects who consent to participate in PK sampling, it is recommended that a separate venous catheter for PK sample collection be placed contralateral to the catheter used for study drug infusion.

NOTE: The catheter that is used for study drug infusion and the arm it is inserted in cannot be used for collection of the PK samples.

5.2 Identity of Investigational Product

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single-use, packaged combination of Cefazolin Sodium USP and iso-osmotic diluent in a DUPLEX container. The DUPLEX container is a flexible dual-chamber container. Cefazolin Sodium USP (active ingredient) is supplied in the drug chamber as a lyophilized form equivalent to 1 g or 2 g of cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.

In pre-reconstituted form, the cefazolin appears as a white or almost white powder and the dextrose is a clear fluid. When reconstituted, the prepared solution is clear.

B. Braun Medical Inc. or its designee will provide to the study sites directly adequate supplies of the study drugs. The following drug supplies will be used in the study:

Product[1]	Strength	Diluent	Route
Cefazolin Sodium USP	1 g	4% Dextrose Injection USP, 50 mL	Intravenous
Cefazolin Sodium USP	2 g	3% Dextrose Injection USP, 50 mL	Intravenous

Abbreviation: USP, United States Pharmacopeia.

[1] Supplied as a lyophilized form for injection in the DUPLEX container.

5.3 Management of Clinical Supplies

5.3.1 Study Drug Packaging and Storage

Cefazolin for Injection USP and Dextrose Injection USP will be manufactured in the DUPLEX container and shipped by the sponsor or its designee. Each DUPLEX container will contain a dosage for 1 subject.

Study drug must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at controlled room temperature according to the storage conditions on the label (20°C to 25°C [68°F to 77°F]) and in the investigator's brochure. After reconstitution (activation), study drug must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

A label will be attached to each subject's study drug. Each label will bear the following information:

- Study drug name
- Dosage (1g or 2g)
- Lot number
- Expiration date
- Storage requirements
- Investigational new drug statement in accordance with US Title 21 Code of Federal Regulations (CFR) Subpart A 312.6, as required

- Name and address of the sponsor

Further details and written instructions may be provided by the study site monitor prior to or at study initiation. Labels may have additional information or modifications as required to meet local regulations.

5.3.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt and storage conditions. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Treatment compliance will be determined based on the amount of study drug used by each subject (Section 5.6). At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.3.3 Other Supplies

Instructions and materials for collection, processing, storage, and shipping of clinical and PK laboratory samples to be analyzed at the central laboratory will be provided to the study sites. Instructions will be provided as a separate document.

Other clinical supplies provided to the study sites include CRF completion guidelines, pharmacy manual, and SAE and pregnancy report forms.

5.4 Overdose Management

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the sponsor or its designee. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported in relevant AE/SAE sections in the eCRF.

5.4.1 Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

5.5 Blinding

This is an open-label study.

5.6 Treatment Compliance

Study drug will be administered by trained, qualified personnel designated by the investigator. Study drug will be administered over 30 minutes as an infusion starting 0.5 to 1 hour before surgery begins and following institutional guidelines. The date and time of study drug administration will be documented. The date and time of anesthesia induction will also be documented. Comments will be recorded if there are any deviations from the planned administration procedures. All study assessments will be performed by qualified study personnel and recorded in subject eCRFs. Compliance may also be ensured by sponsor audit of the source documents, including study subject eCRFs.

5.7 Prior and Concomitant Therapy

Concomitant use of or treatment with any medication (eg, prescription, herbal, OTC medication[s] or dietary supplements) known to interact with cefazolin is prohibited within 5 days prior to the study drug administration until completion of the follow-up visit. Concomitant use of probenecid is also prohibited for this period.

If a subject has an infusion-related reaction due to study drug, the study drug will be discontinued and the subject will not be rechallenged with the study drug. The choice of an alternate antibiotic for surgical prophylaxis will be made by the investigator or designee under the direction of the investigator.

Any acute medication necessary during conduct of the study will be recorded in the eCRF.

Use of all concomitant medications from Screening through completion of follow-up will be recorded in the subject's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications also will be recorded in the subject's eCRF.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects' LARs will sign an ICF. Specified requirements for potential subjects on the informed consent process are detailed in Section 4.1.1. Subjects and their LARs will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject and the subject's LAR. The investigator or designee will also sign the ICF.

Subjects will undergo the study procedures at the time points specified in the schedule of events (Table 3-1).

6.1 Study Visits

6.1.1 Screening Visit (Up to 30 Days Before Study drug Administration)

The Screening Visit will take place within the 30 days before study drug administration (Day –30 to Day –1). The Screening Visit can occur on Day 1 (day of surgery) as long as all Screening Visit assessments are properly completed.

During the Screening Period, subjects will be evaluated by the investigator according to the inclusion and exclusion criteria (Section 4.1) to determine eligibility.

Screening Visit assessments and procedures will include:

- Informed consent for study participation (Section 8.3)
- Informed consent for PK participation (Section 8.3)
- Assignment of SID number
- Demographics:
  - Gender
  - Date of birth
  - Ethnicity (Hispanic/Latino or not Hispanic/not Latino)
  - Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
  - Height (without shoes)
  - Weight (with indoor clothing and without shoes)

- Medical history
- Medication history
- Complete physical examination (Section 6.2.2)
- Vital signs (Section 6.2.3)
- Electrocardiograph (ECG) (Section 6.2.4)
- Clinical laboratory tests (Section 6.4)
- Pregnancy test (Section 6.3)
- Begin concomitant medication documentation

6.1.2 Presurgery Visit (Day 1)

The following assessments and procedures will be performed at the presurgery visit:

- Weight (with indoor clothing and without shoes)
- Updated medical history for eligibility
- Brief physical examination (Section 6.2.2)
- Vital signs (Section 6.2.3)
- Clinical laboratory tests (Section 6.4)
- Pregnancy test (Section 6.3)
- Review of concomitant medications and AE assessments
- Study drug administration (Section 5.1)

6.1.3 Surgery (Day 1)

- Vital signs (Section 6.2.3)
- Study drug infusion site assessment (Section 6.2.5)
- Pharmacokinetic blood sample collection (Section 6.7)
- Review of concomitant medications and AE assessments

6.1.4 Postsurgery Visit (Day 1 or Day 2)

Postsurgery assessments will be performed at 24 hours after surgery or discharge from the study site, whichever comes first.

The following assessments and procedures will be performed at the postsurgery visit:

- Brief physical examination (Section 6.2.2)
- Vital signs (Section 6.2.3)
- Electrocardiograph (Section 6.2.4)
- Study drug infusion site assessment (Section 6.2.5)
- Clinical laboratory tests (Section 6.4)
- Review of concomitant medications and AE assessments

6.1.5 Safety Follow-up Visit (Day 8 [±1 day])

On Day 8 (±1 day), a safety follow-up visit will be performed for safety assessments. Whenever possible, subjects who withdraw prematurely after receiving study drug will also undergo the following safety assessments scheduled for the safety follow-up visit:

- Brief physical examination (Section 6.2.2)
- Vital signs (Section 6.2.3)
- Clinical laboratory tests (Section 6.4)

- Study drug infusion site assessment (Section 6.2.5)
- Review of concomitant medications and AE assessments

6.2 Safety Assessments

Safety will be determined by monitoring AEs, physical examination, vital signs, ECGs, and clinical laboratory tests. Details of laboratory tests are outlined in Section 6.4.

6.2.1 Adverse Events

6.2.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all treatment-emergent AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after beginning study participation if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.2.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the subject signs the ICF until exit from the study.

Serious AEs, brought to the investigator's attention after the subject has completed the study, need **NOT** be reported unless the investigator considers them related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs identified from any study data (eg, laboratory values, physical examination findings, vital sign changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

6.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes study drug administered, dose, event term, date of onset and resolution, exact time of onset only for events occurring on day of surgery, investigator-specified assessment of severity and relationship to study drug, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed up to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.2.1.1) must be reported to the sponsor or their designee immediately (ie, within 24 hours) after the time that study site personnel first learn about the event. The following contact information is to be used for SAE reporting:

PPD Pharmacovigilance:

24 Hour Safety Hotline **phone number**: +1 800 201 8725

24 Hour Safety Hotline **fax number**: +1 888 488 9697

6.2.1.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: An event usually transient in nature and generally not interfering with normal activities. Minimal or no treatment is indicated.

Moderate: An AE that is sufficiently discomforting to interfere with normal activities. Treatment may be necessary.

Severe: An AE that is incapacitating and prevents normal activities. Systemic drug therapy or other treatment may be necessary.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is readministered.

6.2.1.6 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the relevant page in the eCRF and followed up to satisfactory resolution. For the purposes of this study, satisfactory resolution means that the investigator deems the event to be chronic or not clinically significant, or considers the subject to be stable.

6.2.2 Physical Examination

Complete physical examination will be performed at Screening by the investigator or a delegate.

The complete physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph

nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

A brief physical examination will be performed by the investigator or a delegate both before and after dosing on Day 1 and at the follow-up visit (Table 3-1).

It is preferred that the same clinician conduct all physical exams on any single subject.

All treatment-emergent findings that were not present at Screening or described in medical history will be reported in the eCRF.

6.2.3 Vital Signs

Vital signs (including blood pressure [systolic and diastolic], pulse, body temperature, and respiratory rate) should be taken with subjects in supine position after resting for 5 minutes. The vital signs will be measured and assessed at Screening, Day 1, and at the follow-up visit on Day 8 (±1 day) (Table 3-1). Pre-surgery vital sign measurements should be obtained within approximately 30 minutes before the start of study drug administration. Time points for vital sign measurements on Day 1 are pre-surgery, 15 minutes [±5 minutes], 0.5 to 1.0 hour, and 3.0 hours [±15minutes] after the start of the study drug infusion, and after surgery as specified in Table 3-1.

6.2.4 Electrocardiograph

Electrocardiographs will be performed at Screening and post-surgery as specified in the Schedule of Events (Table 3-1). Subjects should be resting quietly in fully supine position for 5 minutes before the ECG recording. Clinical review and assessment of cardiac rhythm, conduction, waveform morphology and ECG interval duration will be performed at the study site, as close as possible to the time an ECG was obtained, by the investigator or his/her designee.

6.2.5 Infusion Site Assessments

The site of study drug infusion will be evaluated for signs of infusion-related reactions on Day 1, and at the follow-up visit on Day 8 (±1 day). Day 1 infusion site assessments are at 15 minutes (±5 minutes), 0.5 to 1.0 hour, 3.0 hours (±15minutes) after the start of the study drug infusion, and post-surgery as listed in the Schedule of Events (Table 3-1).

6.3 Pregnancy

Female subjects who are known to be pregnant should not be enrolled in the study. All female subjects of childbearing potential will have a urine pregnancy test at Screening and on Day 1 (presurgery). If positive, pregnancy will be confirmed with a serum test. If pregnancy is confirmed, the subject will not be enrolled, or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to B. Braun Medical Inc. or its designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study drug must be promptly reported to B. Braun Medical Inc. or its designee.

Females of childbearing potential will be required to use an effective method of birth control as determined by the investigator from Screening period until exit from the study. Effective methods of birth control may include oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy.

6.4 Clinical Laboratory Analyses

Laboratory tests except for screening procedures will be performed by the central laboratory. Screening laboratory tests should be performed within 30 days of Day 1 and can be the same tests as assessed for surgical clearance. Screening laboratory tests will be performed at local laboratories. Aliquots of the serum and plasma collected at Screening will be sent to the central laboratory for replicate analysis and will serve as the baseline laboratory values.

Blood samples for clinical laboratory assessments and urine samples for pregnancy testing will be collected at the time points specified in Table 3-1.

The following laboratory analyses will be performed:

Hematology	Clinical Chemistry
• Hemoglobin • Hematocrit • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Platelets • Red blood cell • White blood cell with differential count	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen • Serum creatinine[1] • Total bilirubin • Sodium • Potassium • Chloride • Bicarbonate • Glucose • Uric acid • Calcium • Phosphate • Total protein • Creatine phosphokinase (CPK) • Lactic acid dehydrogenase (LDH)

[1] At Screening, serum creatinine performed within 3 months of the planned surgical procedure will be accepted if the subject was in stable medical condition at the time of the test and has remained in stable medical condition since the test was performed.

Urine pregnancy tests will be performed for all females of childbearing potential at Screening and be repeated on Day 1. If positive, pregnancy will be confirmed with serum test (Table 3-1). If pregnancy is confirmed, the subject will not be enrolled, or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

Any abnormal laboratory test results (hematology and clinical chemistry) or other safety assessments (eg, physical examination and vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

6.5 Clinical Laboratory Samples Collection

The blood samples and urine pregnancy samples collected at Screening will be analyzed at local laboratories and will follow standard practices of the study site laboratories. Aliquots of the serum and plasma collected at Screening will be sent to the central laboratory for replicate analysis and will serve as the baseline laboratory values. The amount of blood to be drawn for these clinical laboratory samples will be approximately 32 mL per subject (8 mL × 4 samples). This is aligned with general recommendations for the allowable total blood volume collection in pediatric subjects (Howie 2011). Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

The blood samples collected at Treatment and Follow-up Periods (Days 1 to 8) will be analyzed by the central laboratory. Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

6.6 Pharmacokinetic Analysis

Pharmacokinetic blood samples will be obtained to determine cefazolin plasma concentrations. Cefazolin plasma concentrations will be used to refine the population PK model. The details of the refined population PK model analysis will be contained in a separate report. Plasma samples will be analyzed at a sponsor-approved bioanalytical facility using validated and specific methods.

6.7 Pharmacokinetic Samples Collection

Pharmacokinetic blood samples will be obtained at 0.5 to 1.0 hours, 2.0 hours (±15 minutes), 3.0 hours (± 15 minutes), and 4.0 hours (± 15 minutes) after the start of the study drug infusion. The amount of blood to be drawn for these PK samples will be approximately 16 mL per subject (4 mL × 4 samples). This is aligned with general recommendations for the allowable total blood volume collection in pediatric subjects (Howie 2011). Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

If the surgery is unexpectedly extended beyond the 3-hour limit and an additional dose of study drug will be administered best efforts will be made to obtain the 3-hour and possibly the 4-hour PK samples prior to administration of the additional dose of study drug.

Pharmacokinetic sample collection should not be continued after the administration of an additional dose of study drug. In the cases of an additional dose of study drug, subjects from whom a 3-hour PK sample is obtained prior to administration of the additional dose are considered PK completers.

For subjects who consent to participate in PK sampling, it is recommended that a separate venous catheter for PK sample collection be placed contralateral to the catheter used for study drug infusion.

It is important to note that PK blood samples can NOT be collected from the study drug infusion line nor from the same arm as the study drug infusion.

7 Statistical and Analytical Plan

7.1 Primary Safety Endpoints

Safety will be assessed by monitoring AEs, physical examinations, vital signs, ECGs, and clinical laboratory results.

7.2 Sample Size Determination

Approximately 110 subjects (males and females) will be enrolled in the study. This sample size was determined based on the requirement of the FDA as part of the Pediatric Research Equity Act to evaluate the safety of a single dose of cefazolin for surgical prophylaxis in 100 pediatric subjects using the dose equivalent to 2-g cefazolin exposure in adults.

Additional subjects may be enrolled if necessary to ensure at least 50 evaluable subjects with complete safety data per dose group complete the study.

Approximately 40 subjects (males and females across both dose groups) will be enrolled in the PK subgroup. This sample size was determined using model-based simulations designed to explore both the number of subjects needed and the optimal times at which to obtain PK samples from those subjects. The previously-developed population PK model (Trang et al 2014) was employed using permutations introduced empirically to approximate potential PK differences in children enrolled in this study. Specifically, the previous population PK analysis found that pediatric surgical patients had, on average, 32% slower cefazolin clearance than healthy adult volunteers. The model-based simulations assessed how many subjects would be required to adequately capture the "true" difference in clearance between pediatric surgical subjects and healthy adults if the underlying difference was either greater than previous observation (ie, a 50% decrease in clearance) or less than the previous observation (25%, 10%, or 0% difference). A range of sample sizes and PK sampling schemes were evaluated. Note that optimal sampling schemes were first identified using a multiple linear regression approach and then verified using the model-based simulations.

The results of the model-based simulation analyses indicated that a sample size of 40 subjects, each of which provides 4 blood samples for cefazolin assay at times of 0.5 to 1.0 hours, 2.0 hours 3.0 hours, and 4 hours after the start of the cefazolin infusion, would be expected to provide adequate power to detect the true difference in clearance between pediatric surgical subjects and healthy adult volunteers.

A minimum of 10 of the 40 PK subjects are planned to be in the 10 to 13 years old age bracket to ensure adequate representation of that age bracket in the refined population PK model.

Additional subjects may be enrolled if necessary to ensure complete PK data from at least 40 subjects.

7.3 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Safety analysis set: The safety analysis set will consist of all subjects who received any study drug. All analyses using the safety set will group subjects according to treatment actually received.

Pharmacokinetic analysis set: The pharmacokinetic analysis set will consist of all subjects from whom at least one measurable concentration PK sample is obtained.

7.4 Description of Subgroups To Be Analyzed

No subgroup analyses are planned.

7.5 Statistical Analysis Methodology

Statistical analysis of the safety and PK analyses sets will be performed using SAS® software Version 9.2 or later (SAS Institute Inc, Cary, North Carolina). Descriptive statistics will be presented for all safety parameters. Continuous variables will be summarized by treatment group using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

No inferential statistical analysis will be performed.

Baseline will be defined as the values obtained at Screening.

Baseline demographic and background variables will be summarized by arm and overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.5.1 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. Adverse events will be listed. The number and percentage of subjects experiencing an event will be tabulated by treatment and overall for each system organ class and preferred term. Adverse events will also be tabulated according to severity and causality.

Serious AEs and AEs leading to discontinuation will be listed separately.

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the investigator's assessment on clinical significance. Clinically significant laboratory test abnormalities that were considered AEs by the investigator will be presented in the AE listings.

Clinical laboratory tests (observed and change from baseline) will be summarized descriptively in tabular format.

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital sign findings that were considered AEs by the investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized descriptively in tabular format for individual vital sign measurements.

Individual data listings of ECG results (observed and change from baseline) will be presented for each subject. Individual clinically significant ECG findings that were considered AEs by the investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized by treatment descriptively in tabular format for individual ECG results.

Abnormal physical examination findings will be listed.

7.5.2 Pharmacokinetic Analyses

Cefazolin plasma concentrations will be listed in data listings and summarized using descriptive statistics. Cefazolin plasma concentrations will be used to refine the population PK model. The details of the refined population PK model analysis will be contained in a separate report.

7.5.3 Other Analyses

Summary statistical analyses will be provided for demographics and baseline characteristics.

7.5.4 Interim Analyses

No interim analysis is planned.

7.6 Data Quality Assurance

7.6.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include demographic and medical information for the subject and should be as complete as possible.

Study site personnel will enter subject data in the eCRFs. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA, an internal validated medication dictionary.

After database lock, each study site will receive a compact disk read-only memory (CDROM) containing all of their site-specific eCRF data as entered in the eCRF for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study sites' data from the study will be created and sent to the sponsor for storage.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject and the subject's LAR must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, protocol version and/or date, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Subject Information and Consent

A written informed consent in compliance with 21 CFR 50 shall be obtained from each subject and/or his or her LAR before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. Additional informed consent will be obtained from subjects who agree to participate in the PK subgroup. An informed consent template may be provided by the sponsor or its designee to study sites. If any institution-specific modifications to study-related procedures are proposed to be made by the study site, the consent must be reviewed by the sponsor or its designee or both before IRB

submission. Once reviewed and approved, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects and/or LAR as appropriate must sign the revised form.

Before recruitment and enrollment, each prospective subject and his or her LAR will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject and his or her LAR understand the implications of participating in the study, the subject's LAR will be asked to give consent to participate in the study by signing the ICF and the subject may be asked to sign or orally agree to an age-appropriate assent to participation in the study, in accordance with applicable laws, regulations and institutional review board requirements.

The investigator shall retain the signed original ICF(s) and, if any, assent document and give a copy of the signed original forms to the subject and LAR.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (and the subject's LAR), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor its designee is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- IRB-approved informed consent, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject and the subject's LAR
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be registered at www.clinicaltrials.gov according to the requirement from the FDA before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and may work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, which shall be in the sponsor's sole discretion.

10 Study Management

10.1 Monitoring

10.1.1 External Data Monitoring Committee

No external data monitoring committee is planned for this study.

10.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA) access to all study records.

The investigator should promptly notify the sponsor and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor or its designee.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor.

Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although B. Braun Medical Inc. has every intention of completing the study, B. Braun Medical Inc. reserves the right to discontinue the study at any time for clinical, administrative, or any other reasons.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study

Should the study be terminated and/or the study site closed for any reason, all documentation pertaining to the study must be returned to the sponsor.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

The study results will be posted on the clinical trial registry: www.clinicaltrials.gov.

11 Reference List

Ancef (cefazolin for injection) [package insert]. GlaxoSmithKline. Research Triangle Park (NC); 2004 [cited 2016 Jun 08] [11 screens]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/50461slr139_ancef_lbl.pdf

B. Braun Medical Inc. Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX® Container, Investigator's Brochure, 3rd ed. Bethlehem (PA); 2017. 108 p.

B. Braun Medical Inc. (Bethlehem, PA). Single dose study to evaluate the pharmacokinetics of Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Drug Delivery System in pediatric subjects of 10-12 years (inclusive) scheduled for surgery. 2014 Feb 21. Final clinical study report. Protocol No.: HC-G-H-1202. 1001 p.

Cies JJ, Chan S, Hossain J, et al. Influence of body mass index and antibiotic dose on the risk of surgical site infections in pediatric clean orthopedic surgery. Surg Infect (Larchmt). 2012;13(6):371-6.

Haessler D, Reverdy ME, Neidecker J, et al. Antibiotic prophylaxis with cefazolin and gentamicin in cardiac surgery for children less than ten kilograms. J Cardiothorac Vasc Anesth. 2003;17(2):221-5.

Himebauch AS, Sankar WN, Flynn JM, et al. Skeletal muscle and plasma concentrations of cefazolin during complex paediatric spinal surgery. Br J Anaesth. 2016;117(1):87–94.

Howie S. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46–53.

Kamath VH, Cheung JP, Mak KC, et al. Antimicrobial prophylaxis to prevent surgical site infection in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion: 2 doses versus antibiotics till drain removal. Eur Spine J. 2016;25(10):3242–3248.

Khan AJ. Clinical and laboratory evaluation of cefazolin: a new cephalosporin antibiotic in pediatric patients. Curr Ther Res Clin Exp. 1973;15(10):727-33.

Koshida R, Nakashima E, Ichimura F, et al. Comparative distribution kinetics of cefazolin and tobramycin in children. J Pharmacobiodyn. 1987;10(9):436-42.

Koshida R, Nakashima E, Taniguchi N, et al. Prediction of the distribution volumes of cefazolin and tobramycin in obese children based on physiological pharmacokinetic concepts. Pharm Res. 1989;6(6):486-91.

Lee KR, Ring JC, Leggiadro RJ. Prophylactic antibiotic use in pediatric cardiovascular surgery: a survey of current practice. Pediatr Infect Dis J. 1995;14(4):267-9.

Leggett JE, Fantin B, Ebert S, et al. Comparative antibiotic dose-effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. J Infect Dis. 1989;159(2):281-92.

Maher KO, VanDerElzen K, Bove EL, et al. A retrospective review of three antibiotic prophylaxis regimens for pediatric cardiac surgical patients. Ann Thorac Surg. 2002;74(4):1195-200.

Nahata MC, Winters CB, Powell DA. Variation in prophylactic antibiotic use in pediatric orthopedic surgery. Drug Intell Clin Pharm. 1985;19(11):834-6.

Nahata MC, Durrell DE, Ginn-Pease ME, et al. Pharmacokinetics and tissue concentrations of cefazolin in pediatric patients undergoing gastrointestinal surgery. Eur J Drug Metab Pharmacokinet. 1991;16(1):49-52.

Rodgers GL, Fisher MC, Lo A, et al. Study of antibiotic prophylaxis during burn wound debridement in children. J Burn Care Rehabil. 1997;18(4):342-6.

Ross S, Rodriguez W, Khan W. The cephalosporin antibiotics in pediatric practice. South Med J. 1977;70(7):855-61.

Schmitz ML, Blumer JL, Cetnarowski W, et al. Determination of appropriate weight-based cutoffs for empiric cefazolin dosing using data from a phase 1 pharmacokinetics and safety study of cefazolin administered for surgical prophylaxis in pediatric patients aged 10 to 12 years. Antimicrob Agents Chemother. 2015;59(7):4173-80.

Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20(3):629-37.

Smits A, Kulo A, Verbesselt R, et al. Cefazolin plasma protein binding and its covariates in neonates. Eur J Clin Microbiol Infect Dis. 2012;31(12):3359–65.

Trang M, Forrest A, Rubino C. Population PK Analysis for Cefazolin Using Data from HC-G-H-1202: Implications for Dosing in Children, Report from Institute for Clinical Pharmacodynamics for B. Braun Medical Inc. 2014. 72 p.

Yilmaz K, Gunduz Z, Tahan F, et al. Drug rash with eosinophilia and systemic symptoms syndrome induced by cefazolin and gentamicin in a child. HK J Paediatr. (New Series) 2016;21(2):102-104.

12 Appendices

12.1 Package Insert

CEFAZOLIN SODIUM- cefazolin sodium solution
B. Braun Medical Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Cefazolin for Injection USP and Dextrose Injection USP safely and effectively. See full prescribing information for Cefazolin for Injection USP and Dextrose Injection USP.

CEFAZOLIN FOR INJECTION USP AND DEXTROSE INJECTION USP IN DUPLEX® CONTAINER, for intravenous use
Initial U.S. Approval: 1973

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection USP and Dextrose Injection USP and other antibacterial drugs, Cefazolin for Injection USP and Dextrose Injection USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

RECENT MAJOR CHANGES

Dosage and Administration (2) 10/2015

INDICATIONS AND USAGE

Cefazolin for Injection USP and Dextrose Injection USP is a cephalosporin antibacterial indicated in the treatment of the following infections caused by susceptible isolates of the designated microorganisms: Respiratory tract infections (1.1); urinary tract infections (1.2); skin and skin structure infections (1.3); biliary tract infections (1.4); bone and joint infections (1.5); genital infections (1.6); septicemia (1.7); endocarditis (1.8) and perioperative prophylaxis (1.9).

DOSAGE AND ADMINISTRATION

For intravenous use only over approximately 30 minutes. (2)
Use this formulation of cefazolin only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)

Recommended Dosing Schedule in Adult Patients with CrCl Greater Than or Equal To 55 mL/min. (2.1)

Site and Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours
Perioperative prophylaxis	1 gram to 2 grams	½ to 1 hour prior to start of surgery
	500 mg to 1 g	during surgery for lengthy procedures
	500 mg to 1 g	every 6 to 8 hours for 24 hours postoperatively

* In rare instances, doses of up to 12 grams of cefazolin per day have been used.

DOSAGE FORMS AND STRENGTHS

- 1 g in 50 mL and 2 g in 50 mL (3)

CONTRAINDICATIONS

- Hypersensitivity to cefazolin or other cephalosporin class antibacterial drugs, penicillins, or other beta-lactams (4.1)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions: Cross-hypersensitivity may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug. (5.1)
- Use in patients with renal impairment: Dose adjustment required for patients with CrCl less than 55 mL/min. (5.2)
- *Clostridium difficile*-associated diarrhea: May range from mild diarrhea to fatal colitis. Evaluate if diarrhea occurs. (5.3)

ADVERSE REACTIONS

- Most common adverse reactions: gastrointestinal (nausea, vomiting, diarrhea), and allergic reactions (anaphylaxis, urticaria, skin rash). (6)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Probenecid: may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood concentrations. (7)

USE IN SPECIFIC POPULATIONS

- Pediatric use: Cefazolin for Injection USP and Dextrose Injection USP should not be used in pediatric patients who require less than the full adult dose of cefazolin. (8.4)
- Renal impairment: Lower daily dosage of Cefazolin for Injection USP and Dextrose Injection USP is required in patients with impaired renal function (creatinine clearance less than 55 mL/min.) (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin for Injection USP and Dextrose Injection USP and other antibacterial drugs, Cefazolin for Injection USP and Dextrose Injection USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Cefazolin for Injection USP and Dextrose Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria.

1.1 Respiratory Tract Infections

Respiratory tract infections due to *Streptococcus pneumoniae, Staphylococcus aureus* and *Streptococcus pyogenes.*

Injectable benzathine penicillin is considered the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available.

1.2 Urinary Tract Infections

Urinary tract infections due to *Escherichia coli,* and *Proteus mirabilis.*

1.3 Skin and Skin Structure Infections

Skin and skin structure infections due to *S. aureus, S. pyogenes,* and *Streptococcus agalactiae.*

1.4 Biliary Tract Infections

Biliary infections due to *E. coli*, various isolates of streptococci, *P. mirabilis*, and *S. aureus*.

1.5 Bone and Joint Infections

Bone and joint infections due to *S. aureus*.

1.6 Genital Infections

Genital infections due to *E. coli*, and *P. mirabilis*.

1.7 Septicemia

Septicemia due to *S. pneumoniae*, *S. aureus*, *P. mirabilis*, and *E. coli*.

1.8 Endocarditis

Endocarditis due to *S. aureus* and *S. pyogenes*.

1.9 Perioperative Prophylaxis

The prophylactic administration of cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The perioperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Treatment of Indicated Infections in Adults

Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Container should be used only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. The recommended adult dosages are outlined in Table 1. Cefazolin for Injection USP and Dextrose Injection USP should be administered intravenously (IV) over approximately 30 minutes.

Table 1: Recommended Dosing Schedule in Adult Patients with CrCl Greater Than or Equal To 55 mL/min.

Site and Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours

* In rare instances, doses of up to 12 grams of cefazolin per day have been used.

2.2 Dosage for Perioperative Prophylactic Use in Adults

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.

It is important that (i) the preoperative dose be given just prior (1/2 hour to 1 hour) to the start of surgery so that adequate antibacterial concentrations are present in the serum and tissues at the time of initial surgical incision; and (ii) cefazolin be administered, if necessary, at appropriate intervals during surgery to provide sufficient concentrations of the antibacterial drug at the anticipated moments of greatest exposure to infective organisms.

The prophylactic administration of cefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin may be continued for 3 to 5 days following the completion of surgery.

2.3 Dosage in Pediatric Patients

The 2 grams dose of Cefazolin for Injection USP and Dextrose Injection USP is not recommended for use in pediatric patients.

Only administer 1 gram Cefazolin for Injection USP and Dextrose Injection USP to pediatric patients where the individual dose is the entire contents of the 1g DUPLEX® container and not any fraction of it.

Recommended doses for pediatric patients are as follows:

- For most mild to moderately severe infections: a total daily dosage of 25 to 50 mg per kg of body weight, divided into 3 or 4 equal doses.
- For severe infections, the total daily dosage may be increased to 100 mg per kg of body weight.

There are no dosage recommendations for pediatric patients for perioperative prophylaxis or for pediatric patients with renal impairment.

2.4 Dosage in Adult Patients with Renal Impairment

Cefazolin may be used in patients with renal impairment with the dosage adjustments outlined in Table 2. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

Table 2: Dosage Adjustment for Patients with Renal Impairment

Creatinine Clearance	Dose	Frequency
55 mL/min. or greater	full dose	normal frequency
35 to 54 mL/min.	full dose	every 8 hours or longer
11 to 34 mL/min.	1/2 usual dose	every 12 hours
10 mL/min. or less	1/2 usual dose	every 18 to 24 hours

2.5 Preparation for Use of Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX® Container

This reconstituted solution is for intravenous use only.

Do not use plastic containers in series connections. Such use would result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Use only if solution is clear and container and seals are intact.

DUPLEX® Container Storage

- To avoid inadvertent activation, the DUPLEX® Container should remain in the folded position until activation is intended.

Patient Labeling and Drug Powder/Diluent Inspection

- Apply patient-specific label on foil side of container. Use care to avoid activation. Do not cover any portion of foil strip with patient label.
- Unlatch side tab and unfold DUPLEX® Container (see *Diagram 1*).

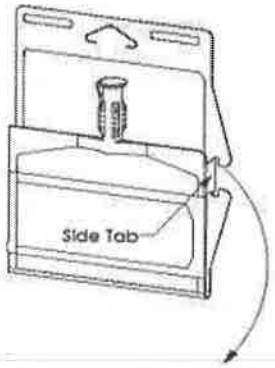


Diagram 1

- Visually inspect diluent chamber for particulate matter.
- Use only if container and seals are intact.
- To inspect the drug powder for foreign matter or discoloration, peel foil strip from drug chamber (see *Diagram 2*).

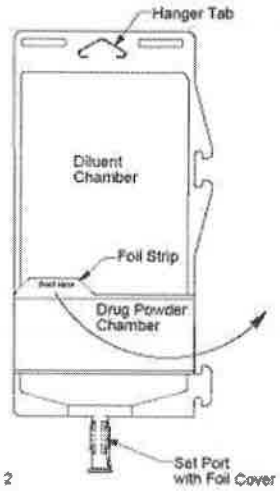


Diagram 2

- Protect from light after removal of foil strip.

Note: If foil strip is removed, the container should be re-folded and the side tab latched until ready to activate. The product must then be used within 7 days, but not beyond the labeled expiration date.

Reconstitution (Activation)

- Do not use directly after storage by refrigeration, allow the product to equilibrate to room temperature before patient use.
- Unfold the DUPLEX® container and point the set port in a downward direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the diluent meniscus trapping all air above the fold. To activate, squeeze the folded diluent chamber until the seal between the diluent and powder opens, releasing diluent into the drug powder chamber (see *Diagram 3*).

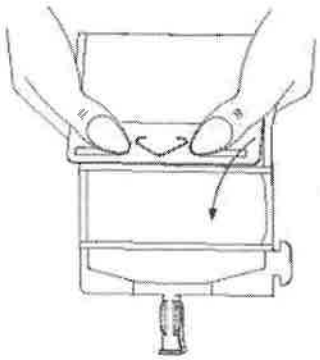


Diagram 3

- Agitate the liquid-powder mixture until the drug powder is completely dissolved.

Note: Following reconstitution (activation), product must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

Administration

- Visually inspect the reconstituted solution for particulate matter.
- Point the set port in a downwards direction. Starting at the hanger tab end, fold the DUPLEX® Container just below the solution meniscus trapping all air above the fold. Squeeze the folded DUPLEX® Container until the seal between reconstituted drug solution and set port opens, releasing liquid to set port (see *Diagram 4*).

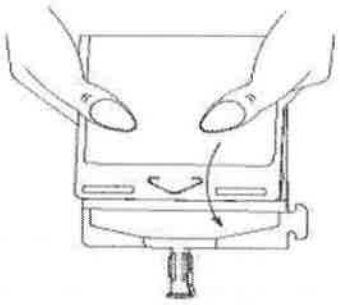


Diagram 4

- Prior to attaching the IV set, check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be compromised.
- Using aseptic technique, peel foil cover from the set port and attach sterile administration set (see *Diagram 5*).

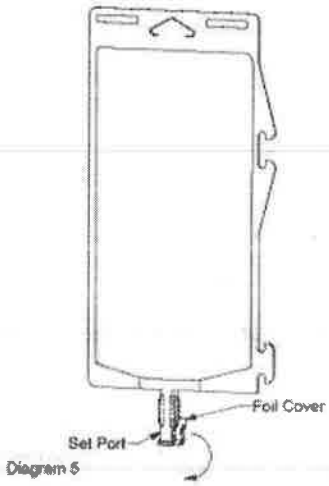


Diagram 5

- Refer to directions for use accompanying the administration set.

Important Administration Instructions

- Do not use in series connections.
- Do not introduce additives into the DUPLEX® Container.
- Administer Cefazolin for Injection USP and Dextrose Injection USP intravenously over approximately 30 minutes.

3 DOSAGE FORMS AND STRENGTHS

Dual-chamber, single-use container:

- 1 g Cefazolin for Injection USP and 50 mL 4% Dextrose Injection USP
- 2 g Cefazolin for Injection USP and 50 mL 3% Dextrose Injection USP

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Cefazolin or the Cephalosporin Class of Antibacterial Drugs, Penicillins, or Other Beta-lactams

Cefazolin for Injection USP and Dextrose Injection USP is contraindicated in patients who have a history of immediate hypersensitivity reactions (e.g., anaphylaxis, serious skin reactions) to cefazolin or the cephalosporin class of antibacterial drugs, penicillins, or other beta-lactams [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions to Cefazolin, Cephalosporins, Penicillins, or Other Beta-lactams

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with Cefazolin for Injection USP and Dextrose Injection USP is instituted, careful inquiry should be made to determine whether the patient has had previous immediate hypersensitivity reactions to cefazolin, cephalosporins, penicillins, or carbapenems. Exercise caution if this product is to be given to penicillin-sensitive patients because cross-hypersensitivity among beta-lactam antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefazolin for Injection USP and Dextrose Injection USP occurs, discontinue the drug.

5.2 Use In Patients with Renal Impairment

As with other beta-lactam antibacterial drugs, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (creatinine clearance less than 55 mL/min.) [see *Dosage and Administration (2.3)*].

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including cefazolin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.4 Hypersensitivity to Dextrose-containing Products

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of dextrose-containing products. These reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose)[1]. The reactions have also been reported when corn-derived dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products.[2]

5.5 Risk of Development of Drug-resistant Bacteria

Prescribing Cefazolin for Injection USP and Dextrose Injection USP in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of Cefazolin for Injection USP and Dextrose Injection USP may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

5.6 Drug/Laboratory Test Interactions

Urinary Glucose

The administration of cefazolin may result in a false-positive reaction with glucose in the urine when using CLINITEST® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (e.g., CLINISTIX®) be used.

Coombs' Test

Positive direct Coombs' tests have been reported during treatment with cefazolin. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibacterial drugs before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

5.7 Patients with Overt or Known Subclinical Diabetes Mellitus or Carbohydrate Intolerance

As with other dextrose-containing solutions, Cefazolin for Injection USP and Dextrose Injection USP should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

6 ADVERSE REACTIONS

The following serious adverse reactions to cefazolin are described below and elsewhere in the labeling:

- Hypersensitivity reactions [see *Warnings and Precautions (5.1)*]
- *Clostridium difficile*-associated diarrhea [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

The following adverse reactions were reported from clinical trials:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), mouth ulcers, vomiting, nausea, stomach cramps, epigastric pain, heartburn, flatus, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment [see *Warnings and Precautions (5.3)*].

Allergic: Anaphylaxis, eosinophilia, urticaria, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions: Pruritus (including genital, vulvar and anal pruritus, genital moniliasis, and vaginitis). Dizziness, fainting, lightheadedness, confusion, weakness, tiredness, hypotension, somnolence and headache.

6.2 Cephalosporin-class Adverse Reactions

In addition to the adverse reactions listed above that have been observed in patients treated with cefazolin, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterials: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

7 DRUG INTERACTIONS

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats, mice and rabbits at doses of 2000, 4000 and 240 mg/kg/day or 1-3 times the maximum recommended human dose on a body surface area basis. There was no evidence of impaired fertility or harm to the fetus due to cefazolin.

8.2 Labor and Delivery

When cefazolin has been administered prior to caesarean section, drug concentrations in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

8.3 Nursing Mothers

Cefazolin is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when Cefazolin for Injection USP and Dextrose Injection USP is administered to a nursing woman.

8.4 Pediatric Use

The 2 g Cefazolin for Injection USP and Dextrose Injection USP is not recommended for use in pediatric patients.

To avoid unintentional overdose, 1 gram Cefazolin for Injection USP and Dextrose Injection USP should only be used in pediatric patients who require the entire contents of the 1 gram dose and not any fraction of it [see *Dosage and Administration (2.3)*].

There are no dosing recommendations for pediatric patients for perioperative prophylaxis or for pediatric patients with renal impairment.

8.5 Geriatric Use

Of the 920 subjects who received cefazolin in clinical studies, 313 (34%) were 65 years and over, while 138 (15%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal

function [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.2)*].

8.6 Patients with Renal Impairment

When Cefazolin for Injection USP and Dextrose Injection USP is administered to patients with low urinary output because of impaired renal function (creatinine clearance less than 55 mL/min.), lower daily dosage is required [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.2)*].

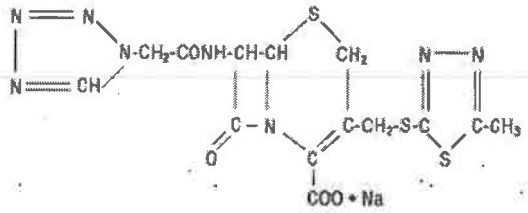
11 DESCRIPTION

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent in the DUPLEX® sterile container. The DUPLEX® Container is a flexible dual chamber container.

After reconstitution the approximate osmolality for Cefazolin for Injection USP and Dextrose Injection USP is 290 mOsmol/kg.

The drug chamber is filled with sterile lyophilized Cefazolin Sodium USP, a semi-synthetic cephalosporin and has the following IUPAC nomenclature: Sodium (6*R*,7*R*)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[2-(1*H*-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

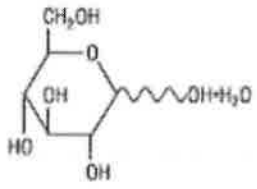
Cefazolin Sodium USP has the following structural formula:



The sodium content is 48 mg/g of cefazolin sodium.

The diluent chamber contains Dextrose Injection USP, an iso-osmotic diluent using Hydrous Dextrose USP in Water for Injection USP. Dextrose Injection USP is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents.

Hydrous Dextrose USP has the following structural (molecular) formula:



The molecular weight of Hydrous Dextrose USP is 198.17

Cefazolin Sodium USP is supplied as a lyophilized form equivalent to either 1 g or 2 g of cefazolin. Dextrose hydrous USP has been added to the diluent to adjust osmolality (approximately 2 g [4.0% w/v] and 1.5 g [3.0% w/v] for the 1 g and 2 g dosages, respectively).

After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use.

Reconstituted solutions of Cefazolin for Injection USP and Dextrose Injection USP range in color from pale yellow to amber.

Not made with natural rubber latex, PVC or DEHP.

The DUPLEX® dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Cefazolin is an antibacterial drug [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

The pharmacokinetic/pharmacodynamic relationship for cefazolin has not been evaluated in patients.

12.3 Pharmacokinetics

Studies have shown that following intravenous administration of cefazolin to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1 g dose.

The serum half-life for cefazolin is approximately 1.8 hours following IV administration.

In a study, using normal volunteers, of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg), cefazolin produced a steady serum concentration at the third hour of approximately 28 mcg/mL.

Plasma pharmacokinetic parameters of cefazolin in normal volunteers (N=12) following a single 15-minute IV infusion of 2 g of Cefazolin for Injection USP and Dextrose Injection USP are summarized in Table 3.

Table 3: Mean (Standard Deviation) Plasma Pharmacokinetic Parameters of Cefazolin in Normal Volunteers

	N	C_{max} (mcg/mL)	T_{max}* (h)	$AUC_{0\text{-}inf}$ (mcg*h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Single 2 g Dose as a 15-Minute IV Infusion	12	280.9 (45.9)	0.25 (0.25-0.33)	509.9 (89.3)	2.01 (0.28)	4.03 (0.68)	11.50 (1.53)

* T_{max} reported as median (range)

N= number of subjects observed; C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve extrapolated to infinity; $t_{1/2}$ = apparent plasma terminal elimination half-life; CL = total clearance; V_z = volume of distribution

Studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum concentrations approximately equivalent to those seen in normal volunteers.

Bile concentrations in patients without obstructive biliary disease can reach or exceed serum concentrations by up to five times; however, in patients with obstructive biliary disease, bile

concentrations of cefazolin are considerably lower than serum concentrations (less than 1.0 mcg/mL).

In synovial fluid, the cefazolin concentration becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours.

12.4 Microbiology

Mechanism of Action

Cefazolin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

Resistance

Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis.

Antimicrobial Activity

Cefazolin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the *INDICATIONS AND USAGE (1)* section.

- Gram-Positive Bacteria
  - *Staphylococcus aureus*
  - *Staphylococcus epidermidis*
  - *Streptococcus agalactiae*
  - *Streptococcus pneumoniae*
  - *Streptococcus pyogenes*

Methicillin-resistant staphylococci are uniformly resistant to cefazolin.

- Gram-Negative Bacteria
  - *Escherichia coli*
  - *Proteus mirabilis*

Most isolates of indole positive Proteus (*Proteus vulgaris*), *Enterobacter* spp., *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp., and *Pseudomonas* spp. are resistant to cefazolin.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standard test [3, 4] (broth and/or agar). The MIC values obtained should be interpreted according to criteria as provided in Table 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters provide reproducible estimates of the

susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be interpreted using a standard test method [4,5]. This procedure uses paper disks impregnated with 30 mcg cefazolin to test the susceptibility of microorganisms to cefazolin. The disk diffusion interpretive criteria are provided in Table 4.

Table 4: Susceptibility Test Interpretive Criteria for Cefazolin*

Pathogen	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤1	2	≥4	-	-	-

* Interpretive criteria are based on 1 g every 8 hr

Abbreviations: S= susceptible, I= intermediate, R= resistant

NOTE: *S. pyogenes* and *S. agalactiae* that have a penicillin MIC of ≤ 0.12 mcg/mL, or disk diffusion zone diameters of ≥ 24 mm with a 10 mcg penicillin disk, may be interpreted as susceptible to cefazolin.

NOTE: Susceptibility of staphylococci to cefazolin may be deduced from testing either cefoxitin or oxacillin.

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where a high dosage of the drug product can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test [3,4,5]. Standard cefazolin powder should provide the following MIC values noted in Table 5. For the diffusion technique using the 30 mcg disk, the criteria in Table 5 should be achieved.

Table 5: Acceptable Quality Control Ranges for Cefazolin

Quality Control Strain	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameters (mm)
E. coli ATCC® 25922	1.0-4.0	21-27
S. aureus ATCC® 29213	0.25-1.0	-
S. aureus ATCC® 25923	-	29-35

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Cefazolin for Injection USP and Dextrose Injection USP have not been performed.

15 REFERENCES

1. Czarny D, Prichard PJ, Fennessy M, Lewis S. Anaphylactoid reaction to 50% solution of dextrose. Med J Aust 1980;2:255-258.
2. Guharoy, SR, Barajas M. Probably Anaphylactic Reaction to Corn-Derived Dextrose Solution. Vet Hum Toxicol 1991;33:609-610.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition.* CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement,* CLSI document M100-S25, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition.* CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX® Container is a flexible dual chamber container supplied in two concentrations. After reconstitution, the concentrations are equivalent to 1 g and 2 g cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP. Dextrose Injection USP has been adjusted to 4.0% and 3.0% for the 1 g and 2 g doses, respectively, such that the reconstituted solution is iso-osmotic.

Cefazolin for Injection USP and Dextrose Injection USP is supplied sterile and nonpyrogenic in the DUPLEX® Container packaged 24 units per case.

NDC	REF	Dose	Volume
0264-3103-11	3103-11	1 g	50 mL
0264-3105-11	3105-11	2 g	50 mL

Store the unactivated unit at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). Do not freeze.

As with other cephalosporins, reconstituted Cefazolin for Injection USP and Dextrose Injection USP tends to darken depending on storage conditions, within the stated recommendations. However, product potency is not adversely affected.

Use only if prepared solution is clear and free from particulate matter.

17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions could occur and that serious reactions require immediate treatment and discontinuation of cefazolin. Patients should report to their health care provider any previous allergic reactions to cefazolin, cephalosporins, penicillins, or other similar antibacterials.

Patients should be advised that diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or

more months after having taken the last dose of the antibacterials. If this occurs, patients should contact a physician as soon as possible.

Patients should be counseled that antibacterial drugs, including Cefazolin for Injection USP and Dextrose Injection USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Cefazolin for Injection USP and Dextrose Injection USP 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 Cefazolin for Injection USP and Dextrose Injection USP or other antibacterial drugs in the future.

Rx only

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ATCC is a registered trademark of American Type Culture Collection.
Clinitest is a registered trademark of Siemens Medical Solutions Diagnostics.
Clinistix is a registered trademark of Bayer Healthcare LLC.

B. Braun Medical Inc.
Bethlehem, PA 18018-3524 USA
1-800-227-2862

Y36-002-906 LD-105-7

PRINCIPAL DISPLAY PANEL - 1g Cefazolin

Cefazolin for Injection USP and Dextrose Injection USP

1g*

REF 3103-11
NDC 0264-3103-11

DUPLEX® *CONTAINER*

50 mL

Use only after mixing contents of both chambers.
For IV Use Only Iso-osmotic Single Dose Sterile/Nonpyrogenic

* Contains Cefazolin Sodium USP equivalent to 1 g cefazolin.

Reconstitution: Hold container with set port in a downward direction and fold the diluent chamber just below the solution meniscus. To activate seal, squeeze folded diluent chamber until seal between diluent and drug chamber opens, releasing diluent into drug chamber. Agitate the reconstituted solution until the drug powder is completely dissolved. Fold the container a second time and squeeze until seal between drug chamber and set port opens.

After reconstitution each 50 mL single dose unit contains: Cefazolin for Injection USP (equivalent to 1 g cefazolin) with approx. 2.0 g (4.0% w/v) Hydrous Dextrose USP in Water for Injection USP. Sodium content is 48 mg/g of cefazolin sodium.
Approximate osmolality: 290 mOsmol/kg

Prior to Reconstitution: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Use only if container and seals are intact. Do not peel foil strip until ready for use. After foil strip removal, product must be used within 7 days, but not beyond the labeled expiration date. Protect from light after removal of foil strip.

After Reconstitution: Use only if prepared solution is clear and free from particulate matter. Use

within 24 hours if stored at room temperature or within 7 days if stored under refrigeration. Do not use in a series connection. Do not introduce additives into this container. Prior to administration check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired. Do not freeze.

Not made with natural rubber latex, PVC or DEHP.

B. Braun Medical Inc.

Bethlehem, PA 18018-3524

Rx only

Produced in USA with API from Italy.

LD-201-6
Y37-002-511

PEEL HERE

Drug Chamber
Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.
See package insert for complete directions for reconstitution and administration.
LD-336-1 X27-001-485

PEEL HERE

Drug Chamber

Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.

See package insert for complete directions for reconstitution and administration.

LD-336-1 X27-001-485

PRINCIPAL DISPLAY PANEL - 2g Cefazolin

Cefazolin for Injection USP and Dextrose Injection USP

2g*

REF 3105-11
NDC 0264-3105-11

DUPLEX® *CONTAINER*

50 mL

Use only after mixing contents of both chambers.
For IV Use Only Iso-osmotic Single Dose Sterile/Nonpyrogenic

* Contains Cefazolin Sodium USP equivalent to 2 g cefazolin.

Reconstitution: Hold container with set port in a downward direction and fold the diluent chamber just below the solution meniscus. To activate seal, squeeze folded diluent chamber until seal between diluent and drug chamber opens, releasing diluent into drug chamber. Agitate the reconstituted solution until the drug powder is completely dissolved. Fold the container a second time and squeeze until seal between drug chamber and set port opens.

After reconstitution each 50 mL single dose unit contains: Cefazolin for Injection USP (equivalent to 2 g cefazolin) with approx. 1.5 g (3.0% w/v) Hydrous Dextrose USP in Water for Injection USP. Sodium content is 48 mg/g of cefazolin sodium.
Approximate osmolality: 290 mOsmol/kg

Prior to Reconstitution: Store at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Use only if container and seals are intact. Do not peel foil strip until ready for use. After foil strip removal, product must be used within 7 days, but not beyond the labeled expiration date. Protect from light after removal of foil strip.

After Reconstitution: Use only if prepared solution is clear and free from particulate matter. Use within 24 hours if stored at room temperature or within 7 days if stored under refrigeration. Do not use in a series connection. Do not introduce additives into this container. Prior to administration check for minute leaks by squeezing container firmly. If leaks are found, discard container and solution as sterility may be impaired. Do not freeze.

Not made with natural rubber latex, PVC or DEHP.

B. Braun Medical Inc.

Bethlehem, PA 18018-3524

Rx only

Produced in USA with API from Italy.

LD-200-3
Y37-002-507

PEEL HERE

Drug Chamber
Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.
See package insert for complete directions for reconstitution and administration.
LD-336-1 X27-001-485

[redacted]

PEEL HERE

Drug Chamber

Discard unit if foil strip is damaged. Peel foil strip only when ready for use. Visually inspect drug prior to reconstitution.

See package insert for complete directions for reconstitution and administration.

LD-336-1 X27-001-485

CEFAZOLIN SODIUM

cefazolin sodium solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0264-3103
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
CEFAZOLIN SODIUM (UNII: P380M0454Z) (CEFAZOLIN - UNII:HS69L0Y4T)	CEFAZOLIN	1 g in 50 mL

Inactive Ingredients	
Ingredient Name	Strength
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	2 g in 50 mL
WATER (UNII: 059QF0KO0R)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0264-3103-11	24 in 1 CASE	07/27/2000	
1		50 mL in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050779	07/27/2000	

CEFAZOLIN SODIUM
cefazolin sodium solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0264-3105
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CEFAZOLIN SODIUM (UNII: P380M0454Z) (CEFAZOLIN - UNII:HS69L0Y4T)	CEFAZOLIN	2 g in 50 mL

Inactive Ingredients

Ingredient Name	Strength
DEXTROSE MONOHYDRATE (UNII: LX22YL083G)	1.5 g in 50 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0264-3105-11	24 in 1 CASE	01/13/2012	
1		50 mL in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050779	01/13/2012	

Labeler - B. Braun Medical Inc. (002397347)