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RESEARCH**

APPLICATION NUMBER:

211413Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY
REVIEW(S)

**Division of Anti-Infective Products
Clinical Microbiology Review**

NDA-211413
SDN 1,2,3,4
Name of the Product: Cefazolin for injection

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Date Review Completed: 09/12/2018

NDA, 505(b)(2): 211413

Date Company Submitted: 12/21/2017
Date received by CDER: 12/21/2017
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Date Completed: 09/12/2018

Reviewer: **Jalal Sheikh, Ph.D.**

NAME OF THE APPLICANT: HQ Specialty Pharma Corp, Paramus, NJ, USA.

DRUG PRODUCT NAMES: Cefazolin for injection, USP

DRUG CATEGORY: Antibacterial

PROPOSED DOSAGE FORM AND STRENGTH: Cefazolin for Injection for intravenous use is supplied in a vial which contains cefazolin sodium equivalent to 2 grams of cefazolin.

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

Perioperative prophylaxis:

- 1 to 2 grams administered ½ hour to 1 hour prior to the start of surgery;
- 500 mg to 1 gram during surgery for lengthy procedures;
- 500 mg to 1 gram every 6 to 8 hours for 24 hours postoperatively.

DISPENSED: Prescription product (Rx)

PROPOSED INDICATION: Cefazolin for Injection is a cephalosporin antibacterial indicated in perioperative prophylaxis.

RELATED DOCUMENTS:

PIND-131420
NDA-050461
NDA-050779

TYPE OF SUBMISSION:

New Drug Application, 505(b)(2)

PURPOSE OF SUBMISSION: Original Application

REMARKS: Cefazolin was first approved by the FDA and marketed in the US in 1978 by GlaxoSmithKline (GSK) under the trade name Ancef (NDA 050461). Ancef has been

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marketed in the dosage strengths of 250 mg, 500 mg, 1 gram, 5 g and 10 g but the product was discontinued. Currently, Cefazolin is marketed in the US by BBraun Medical Inc. and is approved in the United States under NDA 050779.

The Applicant of this NDA, HQ Specialty Pharma provided their rationale for the development of this formulation which is as follows (copied as verbatim from the submission):

Currently, the Reference Listed Drug (RLD) Cefazolin for Injection USP and Dextrose Injection USP is marketed in United States by BBraun Medical Inc. and is approved in United States under NDA 050779.1 The proposed HQ Cefazolin for Injection is similar to the RLD strength, indication, dosing but contains a different formulation matrix. The current RLD is diluted in dextrose while the proposed product can be diluted in various diluents based on patient needs.

Cefazolin is a 1st generation cephalosporin for parenteral use in various infections caused by susceptible organisms as well as for perioperative prophylaxis. However, in clinical practice for a considerable number of indications, daily doses up to 12 g cefazolin (divided into 3 or 4 doses applied every 6 or 8 h) are administered. Moreover, in patients with higher body weight (> 80 kg), the dose in standard indications such as preoperative infection prophylaxis is 2 g as a single dose according to US recommendations. Therefore, an additional formulation providing 2 g cefazolin per vial appears highly valuable in clinical practice.

The cefazolin 2 g per vial formulation allows an easier handling of the drug in the higher dosing range, as only half the numbers of vials have to be reconstituted with solvent. This reduction in vial handlings minimizes the risk for handling errors, such as choice of inappropriate fluid volume or (partly) missed doses. Moreover, the reduced number of sterile vials to be reconstituted reduces to the same amount the risk for inadvertent non-sterile drug administration.

Difference between HQ's cefazolin for injection with BBraun and GSK products:

The differences between HQ's proposed product and the current product on the market are listed below in TABLE 1.

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Table 1: Comparison of BBraun, GSK and HQ's Cefazolin for Injections

Parameter	BBraun- Cefazolin for Injection & Dextrose	GSK – Cefazolin (Discontinued)	HQ's Cefazolin injection, powder	Comments
Brand Name	N/A	ANCEF	N/A	N/A
Active Ingredient	Cefazolin Sodium	Cefazolin Sodium	Cefazolin Sodium	No change
In-active Ingredient	Dextrose	Various diluents (see below)	Various diluents (see below)	proposed product is powder filled vial to be reconstituted with various diluents
Container	BBraun Duplex Bag	Glass Vial	Glass Vial	Different container closure system from RLD
Formulation	BBraun Duplex Bag with powder and diluent in separate chambers	Powder	Powder	Products must be reconstituted prior to use
Diluents	Dextrose	<ul style="list-style-type: none"> - Sodium Chloride Injection, USP - 5% or 10% Dextrose Injection, USP - 5% Dextrose in Lactated Ringer's Injection, USP - 5% Dextrose and 0.9% Sodium Chloride Injection, USP - 5% Dextrose and 0.45% Sodium Chloride Injection, USP - 5% Dextrose and 0.2% Sodium Chloride Injection, USP - Lactated Ringer's 	<ul style="list-style-type: none"> - Sodium Chloride Injection, USP - 5% (b) (4) Dextrose Injection, USP 	Possible diluents will be based on the previously approved Ancef diluents; not only Dextrose as used by BBraun.

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(b) (4) Resistance

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

(b) (4) Antimicrobial Activity

Cefazolin has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [*see Indications and Usage (1)*]:

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 Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: <https://www.fda.gov/STIC>.

SIGNATURES:

Jalal Sheikh, Ph.D.

Clinical Microbiology Reviewer

CDER/OAP/DAIP

September 12, 2018

Concurrence:

Avery Goodwin, Ph.D.

Acting Clin Micro Team Lead

September 12, 2018

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

/s/

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09/12/2018

AVERY C GOODWIN
09/12/2018