CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-817

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7-29-08

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

TO: Division File

SUBJECT: Deputy Division Director's Summary Review Memo for the resubmission of NDA 50-817, cefepime injection in GALAXY Container

1.0 Background

This is the 2nd cycle for this 505(b)(2) application for cefepime injection in GALAXY container. The applicant responded to the action letter of December 21, 2007 on February 1, 2008. Please refer to my summary memo of 12/21/07 for further details regarding the 1st cycle review. In brief, the application received an approvable for issues related to product quality microbiology; specifically, that the applicant had failed to identify the equipment to be used for ——— b(4)
——— of the drug product and its location within the manufacturing facility, and failed to provide the methodology and acceptance criteria for filter integrity testing. In addition, there were deficiencies identified with the drug master file (DMF). The recommended action from the statistical and clinical reviewers was also for an approvable, however the reason cited was an ongoing internal review of a published meta-analysis by Yahav et al. that noted a finding of higher all-cause mortality among subjects who received cefepime monotherapy for febrile neutropenia compared to those who received a comparator beta-lactam antibacterial. I did not concur with that rationale for taking an approvable action because we had not made any changes to the innovator's (Bristol-Myers Squibb) product label for MAXIPIME at that time. The current status of our review of the aforementioned meta-analysis is that data from febrile studies have been submitted by BMS and those datasets are being analyzed. In addition, BMS has been requested to reproduce or refute the findings of the meta-analysis using all studies for which they have access to data.

This memo will summarize elements of reviews that were necessary to evaluate the resubmission, specifically product quality microbiology and clinical.

2.0 Summary of Product Quality Microbiology

The sterility assurance reviewer, Stephen Langille, PhD, has recommended approval because product quality deficiencies have been adequately addressed. Baxter has provided information regarding the following:

- methodology and acceptance criteria for post-filtration integrity testing
- a list of equipment used to manufacture cefepime injection in GALAXY containers including identification numbers and room numbers where the equipment is located and a list of all [redacted] which will be used to manufacture the drug product b(4)

In addition, the deficiencies identified in DMF 6344 have been adequately addressed.

3.0 Clinical Summary

The applicant submitted a safety update as required which consisted of nine relevant publications. No new safety information was provided from these studies. Please refer to Dr. Alma Davidson's clinical review for further information. Of note, one retrospective study that evaluated clinical outcomes in patients with gram-negative bacteremia treated with cefepime suggested that the breakpoints for cefepime for these organisms may be updated. Communication with BMS in this regard has been initiated. The recommended action of Dr. Davidson is an approvable because of the outstanding safety issue related to the meta-analysis. However, the secondary clinical reviewer, Dr. Sumati Nambiar has recommended an approval as no action for the innovator product has been taken because the Agency review of this matter is still ongoing.

4.0 Summary of Labeling Changes

The product label is in PLR format, while that of MAXIPIME is not. Minor changes include updated language with regard to *Clostridium difficile* associated diarrhea as has been made to the RLD label, and DOSAGE AND ADMINISTRATION and Pediatric Use subsection of PRECAUTIONS state that cefepime injection in GALAXY container should only be used in pediatric patients who require the entire 1 or 2 g dose and not any fraction thereof.

5.0 Recommendation

As the product quality deficiencies have been adequately addressed, I recommend an approval for this application.

Katherine A. Laessig, M.D.

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/s/

Kathrine Laessig
8/5/2008 10:18:37 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12-21-07

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

TO: Division File

SUBJECT: Deputy Division Director's Summary Review Memo for NDA 50-817, cefepime injection in GALAXY Container

1.0 Background

Cefepime is an injectable, semi-synthetic cephalosporin in the β-lactam class of antibacterial agents. Its mechanism of action is bactericidal via inhibition of cell wall synthesis by binding to penicillin-binding proteins found in the bacterial cell wall of both Gram-positive and Gram-negative bacteria. The applicant, Baxter Healthcare Corporation, has submitted NDA 50-817 in support of 1 and 2 g injection in GALAXY containers. These premixed products are packaged in GALAXY flexible plastic containers. This application is submitted under Section 505(b)(2) of the FD&C Act, contains no new clinical studies, and relies on the Agency's previous finding of safety and effectiveness for the reference listed drug product, cefepime hydrochloride (MAXIPIME™, NDA 50-679, approved 1/18/96).

The indications for which the applicant is seeking approval are identical to those approved for MAXIPIME and are:

- treatment of pneumonia caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species
- empiric therapy for febrile neutropenic patients
- uncomplicated and complicated urinary tract infection (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate,

including cases associated with concurrent bacteremia with these microorganisms
- uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*
- complicated intra-abdominal infections (used in combination with metronidazole) caused by *Escherichia coli*, *viridans group streptococci*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Enterobacter* species, or *Bacteriodes fragilis*

This memo will summarize elements of all reviews by discipline. For detailed discussions, please refer to the respective CMC, product quality microbiology, pharmacology/toxicology, microbiology, clinical pharmacology, clinical, and biometrics reviews.

2.0 Summary of Chemistry, Manufacturing, and Controls

This application is recommended for approval by the CMC reviewer, Milton J. Sloan, PhD. Baxter's premixed cefepime injection product is a sterile, injectable, iso-osmotic solution of cefepime hydrochloride, USP, dextrose ——, USP, L-arginine, USP, and water for infection, USP, packaged in Baxter's PL 2040 Plastic (GALAXY) container-closure system. It is packaged as 1 g per 50 mL and 2 g per 100 mL. The drug product is stable throughout the proposed shelf life of —— rozen at or below -20 degrees Celsius plus 7 days under refrigeration at 5 degrees Celsius or 24 hours at room temperature (25 degrees Celsius). The manufacturing sites have all been found acceptable by the Office of Compliance. b(4)

3.0 Summary of Product Quality Microbiology

The sterility assurance reviewer, Stephen Langille, PhD, has recommended an approvable action because deficiencies have been identified with the application, as follows:

- The applicant failed to identify the equipment to be used for —— of the drug product and its location within the manufacturing facility b(4)
- The applicant failed to provide the methodology and acceptance criteria for filter integrity testing

The deficiencies in the product quality could result in microbial contamination of the product and therefore the application does not contain adequate information for an approval at this time. Deficiencies were also noted in the DMF such that information supporting the manufacture of Cefepime Injection at the Round Lake facility was inadequate.

4.0 Summary of Pharmacology/Toxicology

Based on the review of the nonclinical pharmacology and toxicology by Dr. Amy Ellis, this application is recommended for approval. Key findings of her review include: 1) the presence of different impurities and degradation products in Cefepime Injection in GALAXY Container did not alter its toxicity profile in comparison to MAXIPIME under the conditions of these studies, 2) Cefepime Injection in GALAXY Container is expected to have a safety profile identical to that of MAXIPIME, 3) the label should be updated such that dose comparisons between the results of the animal reproduction toxicity studies and the current maximum clinical daily dose are accurate, and 4) the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label should be updated to reflect actual results.

5.0 Summary of Clinical Pharmacology

The application is recommended for approval by Jeffrey Tworzyanski, PharmD. No bioequivalence or bioavailability data were included in this application because Cefepime Injection in GALAXY Container contains the same active and inactive ingredients as the RLD MAXIPIME, and it is a parenteral solution for administration by injection. Also, the dosing regimen (frequency and duration) is identical to MAXIPIME when reconstituted for IV administration.

6.0 Summary of Clinical Microbiology

This application is recommended for approval by the clinical microbiology reviewer, Avery Goodwin, PhD. There are no new microbiology data contained in this application. However, he recommends that the microbiology section of the package insert be revised to reflect current CLSI guidelines. Additionally, the organism [redacted] was omitted from the second list since the genus *Enterobacter* is present in the first list. Disk diffusion testing of *S. pneumoniae* can be unreliable when conducted with a [redacted], therefore, disk diffusion susceptibility testing should be done with an oxacillin disk. b(4)

7.0 Summary of Efficacy

No new clinical trial information is submitted as part of this application, therefore there are no statistical analyses or conclusions pertinent to this memo. However, the statistical reviewer, Yan Wang, PhD, recommends an approvable action because of the results of a recently published meta-analysis, which is discussed in the next section of this memo.

8.0 Summary of Safety

There are no new clinical data submitted in this application. However the applicant has conducted a review of the literature from 2002 and concluded that

the safety and effectiveness of Baxter's Cefepime for Injection in GALAXY Container are adequately reflected in the proposed labeling. The Applicant also submitted a safety update which contained additional more recent publications. Of note is a meta-analysis by Yahav et al. that was published in the journal Lancet Infectious Diseases in May 2007. In this article, the authors have reviewed all randomized controlled trials in which cefepime monotherapy was compared to another beta-lactam antibiotic. The primary outcome assessed was 30-day all-cause mortality and a finding of higher all-cause mortality for patients treated with cefepime (RR 1.26 [95% CI 1.08-1.49]) was noted compared to patients receiving other beta-lactam antibiotics and in patients with febrile neutropenia receiving cefepime, specifically (RR 1.42 [95% CI 1.09-1.84]). No obvious reason for the finding was apparent, however hypotheses include unrecognized toxicities of cefepime or inadequate antimicrobial efficacy. A primary limitation of the meta-analysis is missing data (approximately 40% of the identified studies), which the authors indicated was not provided by the innovator, Bristol Myers Squibb (BMS).

Reviewers in DAIOP are evaluating these findings, and have been in communication with BMS, to re-analyze available data from BMS-sponsored studies of cefepime. Importantly, no increase in mortality from previous clinical trials conducted by BMS in support of approved indications was apparent at the time of approval of those indications. However, another recent publication by Bhat et al. in the December 2007 issue of Antimicrobial Agents and Chemotherapy suggests that cefepime breakpoints have become outdated and that the breakpoints should be lowered. Once review of these issues is completed, the MAXIPIME label will be revised as needed, and then the Cefepime for Injection in GALAXY Container will be revised as well.

8.0 Summary of Other Regulatory Issues

DMETS has recommended revisions for the container and container labeling, as well as for the carton labeling that have been accepted by the applicant.

As required under FDAAA, the applicant's request for waiver of pediatric studies has been reviewed by the Pediatric Review Committee (PeRC). As MAXIPIME has been studied and is labeled for use in pediatric patients ages 2 months to 16 years for all of the aforementioned indications, pediatric studies are therefore completed for ages 2 months to 16 years. For pediatric patients less than 2 months of age, pediatric studies are waived. The reason for the waiver is that the product is unlikely to have a meaningful therapeutic benefit over other currently available therapy for these indications in this age group, and it is unlikely to be used because it is premixed and must be administered as a full 1 or 2 g dose that is not appropriate for pediatric patients less than 2 months of age.

9.0 Recommendations

Although the clinical and statistical reviewers have recommended an approvable action because of the uncertainty of the outcome of the review of the possible increase in mortality seen with use of cefepime in the meta-analyses referenced above, at this time it is not known if any action will need to be taken with MAXIPIME at all, and therefore I do not concur with that reason for an approvable. However, the product quality microbiology deficiencies represent significant issues, and therefore I recommend an approvable for this application, pending adequate resolution of the deficiencies by the applicant.

Katherine A. Laessig, MD

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/s/

Kathrine Laessig
12/21/2007 02:19:52 PM
MEDICAL OFFICER