

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-817

OTHER REVIEW(S)

**Internal Consult*******Pre-decisional Agency Information*****

To: Kyong Hyon
Project Manager
Division of Anti-Infective and Ophthalmology Products (DAIOP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: August 1, 2008

Re: NDA 50-817, Cefepime Injection in GALAXY Container for intravenous use
Labeling Review

Thank you for forwarding this consult request, dated March 21, 2008, to DDMAC. We have reviewed the draft package insert sent to DDMAC by DAIOP via e-mail on July 30, 2008, and the draft carton and container labels submitted by the applicant to FDA on February 1, 2008. We have the following comments.

INDICATIONS AND USAGE/DOSAGE AND ADMINISTRATION

- The INDICATIONS AND USAGE sections of the draft PI (both Highlights and Full Prescribing Information or FPI) list uncomplicated skin and skin structure infections (caused by methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*) as one of the proposed indications for cefepime, without any limitations as to the severity of the infections. However, dosing is only provided for **moderate to severe** uncomplicated skin and skin structure infections. Will the drug only be indicated for use in moderate to severe infections? If so, we recommend that this limitation be communicated in the INDICATIONS AND USAGE sections. If the drug will be indicated for uncomplicated skin and skin structure infections of any severity, we recommend that dosing be provided for mild infections.
- We recommend that the INDICATIONS AND USAGE section of Highlights specify that cefepime is indicated for use in **moderate to severe** pneumonia, consistent with the FPI.

WARNINGS AND PRECAUTIONS

- This section of Highlights implies that encephalopathy, myoclonus, and seizures only occur in patients with impaired renal function who do not receive a reduced dose of cefepime. However, the FPI states that some cases occurred in patients who did receive a reduced dose. It is possible that companies may use the Highlights section as the brief summary in advertisements or as a basis for fair balance presentations in promotional materials. Therefore, we recommend that the Highlights section be revised to more accurately communicate these risks, consistent with the FPI.
- This section of the FPI warns that cefepime injection should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is not clear why this is the case. Can additional detail be included in this section?

ADVERSE REACTIONS

- We recommend that this section of Highlights communicate the incidence rates of these events.

CLINICAL PHARMACOLOGY

- Table 7 provides average concentrations of cefepime in specific body fluids and tissues. The statement "**The clinical relevance of these data is uncertain at this time**" (emphasis original) appears following the table. This data may be used promotionally to misleadingly imply efficacy of cefepime for types of infections that the drug is not indicated for, or for other misleading purposes. The bolded disclaimer may not be enough to mitigate the misleading impressions created, or may be absent or minimized in promotional pieces. Since the clinical relevance of the data is unknown, we recommend that you consider deletion of the data, or at least deletion of data that is not relevant to the indications for which cefepime will be approved.
- The Microbiology section of the draft PI states "Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases..." These statements suggest that cefepime is very stable in the presence of beta-lactamases, and may be used in promotional materials to imply this. Are the claims supported by adequate evidence?
- The Microbiology section states that "Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria." This phrase is promotional in tone.

CLINICAL STUDIES

- Section 14.2 describes a clinical trial evaluating cefepime for complicated intra-abdominal infections. The section provides data for the "overall clinical cure rate," but does not describe the specific parameters that define a "clinical cure." Will all prescribers understand what endpoints were measured to define a "clinical cure"?

PATIENT COUNSELING INFORMATION

- We recommend that this section include counseling about penicillin cross-sensitivity.

Other Comments

- The draft PI contains the following phrases (bolding added) that minimize the importance of the risks of cefepime, and that do not appear to provide important information to prescribers:
 - “**As with other antimicrobials**, prolonged use of cefepime may result in overgrowth of nonsusceptible microorganisms.”
 - “**Many cephalosporins, including cefepime**, have been associated with a fall in prothrombin activity.”
 - “**As with some other drugs in this class**, encephalopathy . . . myoclonus, and seizures have been reported.”
 - “**As with other cephalosporins**, anaphylaxis including anaphylactic shock. . . have been reported.”

Unless these bolded phrases provide important information to prescribers, we recommend that you consider deleting them.

Container Labels

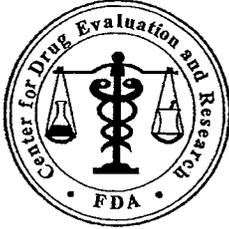
b(4)

We have no comments on these labels.

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/s/

Lynn Panholzer
8/1/2008 02:18:44 PM
DDMAC REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 10, 2008
To: Janice M. Soreth, M.D., Director
Division of Anti-Infective and Ophthalmology Products (DAIOP)
Thru: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh., Director
Division of Medication Error Prevention
From: Kellie Taylor, PharmD, MPH, Team Leader
Division of Medication Error Prevention
Subject: Medication Error Labeling Review for Cefepime Injection in
Galaxy Container
Drug Name(s): Cefepime Injection
Application Type/Number: NDA 50-817
Applicant/sponsor: Baxter Healthcare Corporation
OSE RCM #: 2008-239

1 INTRODUCTION

This memorandum is in response to a February 22, 2008 request from your Division for a review of the revised container labels and _____ for Cefepime Injection from Baxter Healthcare Corporation. b(4)

The Applicant is seeking approval to market Cefepime injection in Galaxy™ Container (PL 2040 Plastic). The proposed presentations are 1 g of Cefepime in 50 mL and 2 g of Cefepime in 100 mL. The products are "ready to use" premixed intravenous formulations and are stored frozen.

The Division of Medication Error Prevention originally reviewed the container labels and carton labeling and forwarded comments to DAIOP on August 24, 2007 (OSE Review 2007-1267). Comments regarding the container labels _____ were included in the Approvable letter sent to Baxter on December 22, 2007. b(4)

2 MATERIAL REVIEWED

The Division of Medication Error Prevention reviewed the revised container labels _____ submitted on February 1, 2008 to determine if the Applicant's revisions were consistent with the changes requested in the Approvable letter and to identify possible improvements to reduce the potential for medication errors. See appendix A for images of the container labels and _____. b(4)

3 DISCUSSION

The Division of Medication Error Prevention notes that the _____ and container labels have been revised in accordance with the recommendations forwarded in the Approvable letter. We did not identify any additional or new areas of concern were identified from a medication errors perspective. b(4)

4 CONCLUSIONS AND RECOMMENDATIONS

Based upon our assessment of the container labels _____, the Division of Medication Error Prevention concludes that the concerns outlined in the Approvable letter regarding the contain labels and carton labeling are fully addressed by the February 1, 2008 resubmission. Please copy our Division on any correspondence to the sponsor pertaining to this memo. If you have any questions or need clarification, contact Cherye Milburn, project manager, at 301-796-2084. b(4)

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Denise Toyer
3/10/2008 03:22:59 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/10/2008 03:26:58 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 24, 2007

To: Janice M. Soreth, M.D.
Director, Division of Anti-Infective and Ophthalmology Products

Thru: Kellie Taylor, Pharm D, MPH, Acting Team Leader
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

From: Richard Abate, RPh, MS Safety Evaluator,
Division of Medication Errors and Technical Support

Subject: Medication Error Labeling Review for Cefepime Injection in
Galaxy Container

Drug Name(s): Cefepime Injection

Application Type/Number: NDA #: 50-817

Applicant/sponsor: Baxter Healthcare Corporation

OSE RCM #: 2007-1267

1 INTRODUCTION

This memorandum is in response to a May 22, 2007 request from your Division for a review of the container labels and _____ for Cefepime Injection from Baxter Healthcare Corporation. The sponsor is seeking approval to market Cefepime injection in Galaxy™ Container (PL 2040 Plastic). The proposed presentations are 1 g of Cefepime in 50 mL and 2 g of Cefepime in 100 mL. The products are “ready to use” premixed intravenous formulations and are stored frozen.

b(4)

2 MATERIAL REVIEWED

DMETS reviewed the container labels and _____ submitted by the sponsor on February 28, 2007 to identify possible improvements to reduce the potential for medication errors.

b(4)

3 DISCUSSION

3.1 GENERAL COMMENTS

Baxter already markets several products in Galaxy™ Containers. DMETS has no concerns with the proposed packaging configuration. However, we do have concerns with “Tall Man” lettering for the established name on the proposed container labels _____

b(4)

3.2 TALL MAN LETTERING

DMETS notes the sponsor has chosen to use “Tall Man” lettering on the container labels and _____ of this product. Tall Man lettering involves highlighting the dissimilar letters in an established or proprietary name to aid in distinguishing between two names that are similar. In addition, the use of Tall Man lettering is generally reserved to distinguish specific pairs of known look-alike medication names. In this case, the sponsor proposed to “Tall Man” the “PIME” portion of Cefepime to distinguish this established name from other cephalosporins.

b(4)

DMETS acknowledges that cephalosporins products are often confused with each other because of similar established names for these products. However, we are concerned that the choice of “PIME” may not be successful in reducing wrong drug errors as several cephalosporins end with “-ime,” such as cefuroxime, cefotaxime, ceftizoxime, and ceftazidime.

The sponsor stated in a teleconference on June 28, 2007 the “Tall Man” letters were arbitrarily chosen and not the subject of any study. The sponsor also stated they received no practitioner input into the selection of these letters to see if they would in fact help differentiate this product from other cephalosporins in their clinical settings. Because this choice of letters was not tested and many cephalosporin products end with “ime,” we are concerned with allowing this “Tall Man” proposal. We are also concerned that arbitrary use of Tall Man lettering has the potential to decrease its effectiveness to distinguish similar name pairs by making this tool more commonplace.

4 CONCLUSIONS AND RECOMMENDATIONS

We acknowledge the similarities among cephalosporin established names. However, we believe “Tall Man” “PIME” will not adequately address these similarities but may increase the similarity as many cephalosporins end with “ime.” We have identified other area of improvement with regard to the container label _____ that should be revised to minimize product selection errors within Baxter’s Galaxy™ Container line. We recommend the following revisions be implemented in the interest of minimizing user error and maximizing patient safety. Please

b(4)

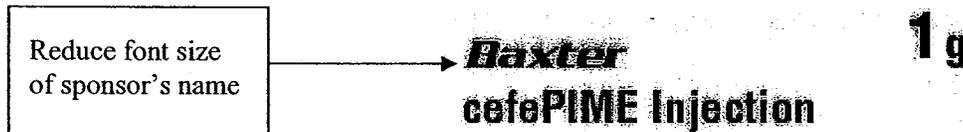
copy DMETS on any correspondence to the sponsor pertaining to this memo. If you have any questions or need clarification, contact Cheryle Milburn, project manager, at 301-796-2084.

4.1 TALL MAN LETTERING

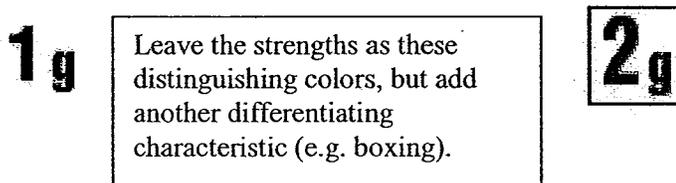
DMETS recommends deleting the use of "Tall Man" lettering on this product and using a standard upper/lower case presentation, e.g. Cefepime Injection.

4.2 CONTAINER LABEL (1 G AND 2 G BAGS)

- A. See Tall Man Lettering 4.1.
- B. The sponsor's name appears as prominently as the established name on the label. Decrease the font of the of the sponsor's name to increase the prominence of the established name.



- C. DMETS notes the sponsor's use of a white background behind the sponsor's name in black print and the established name and product strength in red print on several cephalosporins in the GALAXY™ Container product line. The use of the same color background increases the potential for confusion between cephalosporins in Galaxy™ Containers. DMETS recommends the use of black print for the established name for both strengths of Cefepime for injection to better distinguish this product from the other cephalosporins in Galaxy™ Containers.
- D. The strengths of Cefepime are differentiated by the use of different color print, black for the 1 g bag and red for the 2 g bag. The 2 g bag will also be larger than the 1 g bag. However, the use of the same color background increases the potential for the strengths to be confused. DMETS recommends continued use of black and red to distinguish the strengths (1 g vs. 2 g) as well as using an additional means such as bolding, boxing, or some other means of differentiating the strength to decrease the potential of confusion between the strengths.



4.3

b(4)

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/s/

Richard Abate
8/24/2007 11:06:38 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
8/24/2007 11:28:05 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/24/2007 11:55:31 AM
DRUG SAFETY OFFICE REVIEWER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anti-Infective and Ophthalmology Products

Application Number: NDA 50-817

Name of Drug: Cefepime Injection in GALAXY Container (PL 2040 Plastic)

Applicant: Baxter Healthcare Corporation

Material Reviewed:

Submission Date(s): February 28, 2007

Receipt Date(s): March 1, 2007

Submission Date of Structure Product Labeling (SPL): February 28, 2007

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling and would be forwarded to the Sponsor for addressing.

Highlights

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- Delete _____ above the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section.

b(4)

- The ~~_____~~ statement at the right upper corner of the Highlights page of the label should be deleted. This statement is not required for package insert labeling, only container labels and carton labeling.
- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- The drug name must be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)] Please revise to include route of administration.
- The following statement regarding antibiotic resistance should follow after the initial US approval date. [See 21 CFR 201.24]: "To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria".
- In the table and under DOSAGE AND ADMINISTRATION, an asterisk (*) should not be used to footnote information (an alternate symbol should be chosen) as the asterisk is used in the table of contents to footnote other information.
- Do not include the pregnancy category in Highlights. [See comment #34 Preamble]
- For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval.
- The trade name, "Cefepime Injection in Galaxy Container" in the highlights should not be italic.

b(4)

Full Prescribing Information

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Dosage and Administration (2) and Use in Specific Populations (8.4)] not [see Dosage and Administration (2) and Use in Specific Populations (8), Pediatric Use (8.4)]. Please correct the cross-references throughout the labeling. [See PLR Implementation Guidance]
- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- All text of new paragraphs should consistently be either left justified or indented throughout the labeling.
- The preferred presentation of subsection headings should not be imbedded in the content. For example, the subsection heading "1.1 Pneumonia" should be above the content that it represents. Please correct the subsection headings throughout the labeling.
- Avoid Latin abbreviations because of the greater potential for medication errors should an abbreviation be misread (e.g., QD being misread as QID). For example, q12h should be changed to every 12 hours. Please change all Latin abbreviations throughout the labeling. Refer to the Institute for Safe Medication Practices (ISMP's) website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for list of error-prone abbreviations, symbols, and dose designations.
- Throughout the FULL PRESCRIBING INFORMATION text, the phrases such as

“THAWING OF PLASTIC CONTAINER”, “DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION”, CEFEPIME INJECTION SHOULD BE ADMINISTERED INTRAVENOUSLY OVER APPROXIMATELY 30 MINUTES”, should not be bolded and should not use all capital letters. Use another method for emphasis such as italics or underline.

- The revision date at the end of the highlights replaces the “revision” or “issued” date at the end of the labeling. The revision date should not appear in both places.
- Laboratory Tests and Drug/Laboratory interaction should be under **5 WARNINGS AND PRECAUTIONS** section not under other labeling sections.
- The standard paragraph, “Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.” should be inserted under **6.1 Clinical Studies Experience**.
- Regarding references, are these references necessary? Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- At the end of the labeling, following changes should be made:
 - 1) Unbold the company name
 - 2) Add, “Manufactured by”:, above company name, Baxter Healthcare Corporation.
 - 3) Delete everything starting, “ _____ ” to “Revised November 2006.”

b(4)

Recommendations

The Sponsor would be asked to address the identified deficiencies/issues and re-submit labeling by July 13, 2007 This updated version of labeling will be used for further labeling discussions.

Kyong Hyon, RN, MA
Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

Supervisory Comment/Concurrence:

Frances V. LeSane
Chief, Project Management Staff

Note: The FDA/CDER/OND SEALD Labeling Team (Jeanne Delasko, Consumer Safety Officer, OND) assisted with the development of this Labeling Review.

Drafted: KH/May 7, 2007

Revised/Initialed:

Finalized: June 15, 2007

Filename: CSO Labeling Review Template (updated 1-16-07).doc

Regulatory Project Manager Labeling Review

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CSO LABELING REVIEW OF PLR FORMAT

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/s/

Kyong Hyon
6/25/2007 01:14:41 PM
CSO

Frances LeSane
6/26/2007 05:54:03 PM
CSO