CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-156

MICROBIOLOGY REVIEW(S)

MEMORANDUM

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

DATE: 17 July 2008

TO: NDA 22-156, Cleviprex, The Medicines Company

FROM: Robert J. Mello, Ph.D., Reviewer, New Drug Microbiology Staff

THROUGH: Bryan S. Riley, Ph.D., Senior Reviewer, New Drug Microbiology Staff

cc: Alisea Crowley, Regulatory Project Manager, OND/ODEI/DCRP
Monica Cooper, Chemist, OPS/ONDQA/DPA II
James McVey, Team Leader, New Drug Microbiology Staff
David Hussong, Ph.D., Director, New Drug Microbiology Staff

SUBJECT: Amendment to Microbiology review (dated 29 FEB 2008) for NDA 22-156

The Microbiology Product Quality review of NDA 22-156 for Cleviprex™ (Clevidipine butyrate Injectable Emulsion) dated 29 FEB 2008 concluded that the application was **Approvable** pending receipt of additional information. The single deficiency is shown (in *italics*) below:

Deficiencies:

1. *Labeling that recommends post-penetration reconstituted drug product holding periods ——— must be supported by well defined experimental data that extend beyond the labeled holding period. Therefore, the sponsor should either provide microbiological data supporting the —— holding period following the initial penetration of the stopper or, alternatively, revise the labeling to indicate use within 4 hours following the initial penetration of the stopper.*

On 16 July 2008 the Agency provided to the applicant several comments on the carton and container labeling for the drug product (see below, abstracted from A. Crowley's memo to the file for NDA 22-156, Cleviprex, The Medicines Company dated 17 July 2008).

MEMORANDUM

From: Crowley, Alisea
Sent: Wednesday, July 16, 2008 1:55 PM
To: 'Greg Williams'
Cc: Cooper, Monica; Mello, Robert
Subject: Cleviprex

Hi Greg,

Please see below our preliminary response regarding the carton and container that was submitted on July 1, 2008. Also, we have revised the timeframe to use the Cleviprex product after it has been punctured. The new punctured time will be reflected on [redacted] package insert. If you would like to discuss our comments, we can schedule a short t-con today. The participants would include the chemist and microbiologist. Please let me know as soon as possible.

Thank you,
Alisea

Carton & Container Comments:

[redacted]

The file memo also indicated that the Applicant responded the same day (via email) indicating that they accepted the proposed changes.

With the above change in the drug product's labeling, the application for marketing approval (NDA 22-156) is **Approved** from a microbiology product quality standpoint.

END

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/s/

Robert Mello
7/17/2008 09:40:29 AM
MICROBIOLOGIST

Recommend Approval

Bryan Riley
7/17/2008 09:42:24 AM
MICROBIOLOGIST
I concur.

Product Quality Microbiology Review

29 FEB 2008

NDA: 22-156/N-000

Drug Product Name
Proprietary: Cleviprex™
Non-proprietary: Clevidipine butyrate Injectable Emulsion
Drug Product Priority Classification: S

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
02 JULY 2008	02 JULY 2008	02 DEC 2007	18 JULY 2007
18 APR 2008	21 APR 2008	n/a	n/a

Submission History (for amendments only) N/A

Applicant/Sponsor
Name: The Medicines Company
Address: 8 Campus Drive
Parsippany, NJ 07054
Representative: Gregory C. Williams, Ph.D.
VP Regulatory Affairs and Program Management
Telephone: (973) 647-6010 (phone)
(973) 656-9783
Greg.Williams@THEMEDCO.com

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is approvable pending receipt of additional information (see Section 3).

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** Marketing Authorization

3. **MANUFACTURING SITE:**
Drug Substance: There are two sites.

Drug Product:
Hospira, Inc., 8484 US 70 West, Clayton, NC 27520

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile, injectable oil-in-water emulsion; Intravenous; 0.5mg/ml; Supplied in 50 mL and 100 mL clear glass bottles, fitted with a black rubber stoppers and sealed with an aluminum overseal.

5. **METHOD(S) OF STERILIZATION:**

6. **PHARMACOLOGICAL CATEGORY:** Antihypertensive (calcium channel antagonist)

B. **SUPPORTING/RELATED DOCUMENTS:**
- DMF No Hospira, Inc. (Letter of Authorization, dated MARCH 22, 2007, provided).
- Microbiology Review #1 for NDA 18-449 (15 JAN 2004)

C. **REMARKS:**
- An ONDQA PAL Initial Quality Assessment was entered in to DFS on 27 JULY 2007, and was consulted during this review.
- The application was submitted in "hybrid" electronic CTD format, and the following sections were reviewed:
  - Module 1, Administrative and Prescribing Information
  - Module 2, Section 2.3 Quality Overall Summary
  - Module 3, QUALITY, Section 3.2 S and 3.2 P (Body of Data, Drug Substance and Drug Product).
- The original submission contained
- The drug substance is incorporated into a lipid emulsion identical to 20% INTRALIPID®, a parenteral nutrition product developed by Fresenius-Kabi (now Hospira, Inc.) that received FDA approval under NDA 18-449 (23 JAN 1981).

Filename: N0221156N000R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending receipt of additional information (see Section 3, below).

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a milky-white lipid oil-in-water emulsion. The drug substance is incorporated into the excipients which are the same as the marketed formulation of 20% Intralipid®, developed by Fresenius Kabi (now Hospira). Following formulation, the drug product is filled into either 50 ml or 100ml clear glass bottles fitted with a black —— rubber stoppers and sealed with aluminum overseals.

B. Brief Description of Microbiology Deficiencies - The Sponsor has not provided any microbiological data to support the labeled hold time post-spike entry.

C. Assessment of Risk Due to Microbiology Deficiencies - Cleviprex is a single-use parenteral product that contains phospholipids and can support the growth of microorganisms.

III. Administrative

A. Reviewer's Signature _____
Robert J. Mello, Ph.D.

B. Endorsement Block _____
James McVey

C. CC Block
In DFS

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Robert Mello
4/29/2008 03:13:09 PM
MICROBIOLOGIST

Approvable pending additional information

James McVey
4/30/2008 07:50:41 AM
MICROBIOLOGIST
I concur.