

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-325

OTHER REVIEW(S)

MEMORANDUM

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

DATE: September 29, 2008

TO: Norman Stockbridge, M.D., Ph.D.
Director, Division of Cardiovascular and Renal
Products

Mehul Mehta, Ph.D.
Director, Division of Clinical Pharmacology I

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. CTV 10/01/08
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-325, Nexterone
(Amiodarone Hydrochloride) Injection, 50 mg/mL,
Sponsored by Prism Pharmaceuticals, Inc.

At the request of the Division of Cardiovascular and Renal Products (DCRP) and the Division of Clinical Pharmacology I (DCP1), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: 101

Study Title: "A randomized, double-blind, 2-period crossover trial to determine the relative bioavailability of PM101 I.V. (amiodarone hydrochloride) and Cordarone® I.V. Generic Reference Listed Drug (amiodarone hydrochloride) in healthy adult volunteers"

The clinical and analytical portions of Study 101 were conducted at Anapharm Clinical Laboratory, 5160 boul. Decarie, suite 800, Montreal, Quebec, Canada (Anapharm-Montreal) and at Anapharm, 2500 rue Einstein, Quebec City, Quebec, Canada (Anapharm - Quebec City), respectively. In March 2008, Anapharm-Quebec City

was relocated from 2050 Boul. Rene-Levesque Quest to a new facility at 2500 rue Einstein, Quebec City, Quebec, Canada. Following inspection of the clinical site (September 8 - 12, 2008), FDA Form-483 was not issued and no clinical significant findings were uncovered. Following the inspection of the analytical site (August 21 - 26, 2008) at rue Einstein, Form FDA-483 was issued (Attachment 1). The Form FDA-483 observations and our evaluation follow.

Anapharm, 2500 rue Einstein, Quebec City, Quebec, Canada
(Anapharm-Quebec City)

1. The effect of preparing and processing standard curves and quality control samples (QCs) containing amiodarone (A) and desethylamiodarone (DEA) separately versus those containing A and DEA concomitantly was not evaluated. Specifically, during method validation and production runs, standard curves and QCs of A and DEA were prepared and then processed by spiking each analyte and internal standard into separate blank human plasma, but A and DEA were present concomitantly in study plasma samples.

Anapharm-Quebec City acknowledged this observation and conducted an experiment during the inspection to investigate the issue raised in the 483 observation. The results of the experiment showed that data generated from QC samples containing either A or DEA, and QC samples containing both A and DEA concomitantly (Attachment 2) were accurate (within 8% of the nominal values).

2. Significant DEA concentrations (>5% C_{max}) were found in pre-dose human plasma samples of all subjects in study period two. This finding was not discussed in the analytical report.

DPC1 reviewer should be aware of the significant (>5% C_{max}) pre-dose DEA concentrations observed in study period two (likely due to inadequate wash-out period). During the inspection, Anapharm - Quebec City said that the sponsor did not contract Anapharm-Quebec City to conduct the pharmacokinetic data analysis and they were not sure if the DEA data reported by the Sponsor were corrected for the pre-dose DEA concentrations.

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Injection, 50 mg/ml

Conclusion:

The Division of Scientific Investigations recommends that the data from Study M06-830 be accepted for review. DPC1 reviewer should be aware of the significant pre-dose DEA concentrations observed in all subjects in study period two.

After you have reviewed this memo, please append it to the original NDA submission.

Martin K. Yau, Ph.D.

Final Classification:

VAI: Anapharm 2500 rue Einstein, Quebec City, Quebec, Canada

NAI: Anapharm Clinical Laboratory, 5160 boul. Decarie, suite
800, Montreal, Quebec, Canada

9 Page(s) Withheld

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/s/

Martin Yau
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CSO