DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

August 13, 2004

Dear Members, Consultants, Speakers, and Guests:

Thank you for your willingness to participate in the September 10, 2004 Cardio-Renal Drugs Advisory Committee meeting regarding Exanta® (ximelagatran) Tablets for the following indications:

1. Prevention of venous thromboembolism (VTE) in patients undergoing knee replacement surgery
2. Prevention of stroke and other thromboembolic complications associated with atrial fibrillation
3. Long term secondary prevention of VTE after standard treatment for an episode of acute VTE

We are providing you an Integrated Executive Summary with issues for committee consideration. In this background package, we also provide the draft reviews of the New Drug Application (NDA) from the Food and Drug Administration (FDA) medical, statistical, and Office of Drug Safety reviewers. The FDA background package often includes initial reviews and/or preliminary conclusions and recommendations written by individual FDA reviewers. These conclusions and recommendations do not necessarily represent the final position of the individual reviewer, nor do they necessarily represent the final position of the FDA. The FDA will not take a final action on the application until input from the advisory committee has been considered and all reviews have been finalized.

In order to aid your review of the documents provided by the FDA and AstraZeneca LP, we would like to focus on the following topics:

- Safety of short-term and long-term use, particularly with regard to hepatotoxicity
- Adequacy of the sponsor's proposed risk management program for hepatotoxicity
- Possible increased risk of myocardial infarction/coronary artery disease
- Benefit risk assessment for the use of Exanta (ximelagatran) in each indication

The following items are attached:

1. Integrated Executive Summary
2. Draft Medical Officer Review, Division of Gastrointestinal and Coagulation Drug Products
3. Draft Statistical Review, Division of Biometrics II
4. Draft Medical Officer Review, Division of Cardio-Renal Drug Products
5. Draft Statistical Review, Division of Biometrics I
6. Draft Review, Office of Drug Safety
7. Clinical White Paper, CDER-PhRMA-AASLD Conference, November 2000

The final questions will be given to you prior to the actual meeting.

We look forward to your participation and to a productive meeting on September 10, 2004.

Sincerely,

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration