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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
NDA 17-820/S-037**

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 17-820
Supplement SLR-037

SUBMISSION DATE: August 27, 2001

Dobutrex[®] (Dobutamine) Injection
Eli Lilly and Company
Indianapolis, IN

REVIEWER: Angelica Dorantes, Ph.D

TYPE OF SUBMISSION: Supplemental SLR NDA/Revised Geriatric Labeling

SUBMISSION:

Reference is made to the approved NDA 17-820 for Dobutrex[®] (Dobutamine) Injection. Dobutrex[®] is an agent indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of patients with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

Reference is also made to the Final Rule published in the Federal Register on August 27, 1997, which amends CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs", adding a "Geriatric Use" subsection to the Precautions section of the labeling. In compliance with that Final Rule, supplement SLR-037 to NDA 17-820 dated August 27, 2001, provides a revised labeling that includes information on the use of Dobutrex in elderly patients aged 65 and over. Specifically, the changes are consistent with the draft guidance "Content and Format for Geriatric Labeling" dated December, 1998.

The revised labeling proposes a new "Geriatric Use" subsection under the PRECAUTIONS section using the language recommended by FDA. The proposed geriatric labeling changes are based on clinical data from the original NDA and published clinical literature for dobutamine in elderly patients with heart disease. The number of patients cited in the geriatric section has been taken from the following documents and references:

- The Integrated Summary of Safety information portion; Volume E.8, pages 315,339-343 of the original submission.
- An external study described in: Anthopoulos L, et al. Stress Echocardiography in Elderly Patients With Coronary Artery Disease. *J Am Coll Cardiol* 1996;28:52-9.
- An external study described in: Chenzbraun A, et al. Impact of Age on the Safety and the Hemodynamic Response Pattern During High Dose Dobutamine Echocardiography. *Echocardiography*, Volume 16, February 1999:135-142.

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- An external study described in: Rendard M, et al. Hemodynamic Effects of Dobutamine in Patients below and over 65 years, with Left Heart Failure Secondary to an Acute Myocardial Infarction, *Gerontology* 30:408-413 (1984).
- An external study described in: Poldermans D, et al. Dobutamine-Atropine Stress Echocardiography in Elderly Patients Unable to Perform an Exercise Test. Hemodynamic Characteristics, Safety, and Prognostic Value. *Arch Intern Med.* 1994;154:2681-3686.
- An external study described in: Elhendy A, et al. Safety, Hemodynamic Profile, and Feasibility of Dobutamine Stress Technetium Myocardial Perfusion Single-Photon Emission CT Imaging for Evaluation of Coronary Artery Disease in the Elderly. *CHEST* 2000; 117:649-656.
- An internal study described in: Poldermans D, et al. Cardiac Chronotropic Responsiveness to Beta-Adrenoceptor Stimulation Is Not Reduced in the Elderly. *J Am Coll Cardiol* 1995;25:995-9.

The sponsor states that additional searches of published literature were conducted on February 6, 2001 for the years 1990-2001 (using Medline and Embase), and examination of spontaneously reported adverse event data revealed no additional information regarding the safety and efficacy of Dobutrex in patients aged 65 and older.

The sponsor's proposed text for the "Geriatric Use" subsection is as follows:

Geriatric Use--Of the 1893 patients in clinical studies who were treated with dobutamine, 930 (49.1%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

OCPB LABELING RECOMMENDATION:

1. From the OCPB's viewpoint the revised labeling appears to be appropriate. However due to the clinical nature of the references that were given to support the geriatric information included in the "Geriatric Use" subsection of Dobutrex labeling, OCPB/DPEI is of the opinion that the geriatric information should be reviewed and comment by the medical officer of HFD-110.
2. In addition, it should be noted that the labeling for Dobutrex Injection does not include under the "CLINICAL PHARMACOLOGY" section, a "Pharmacokinetic" subsection. Therefore, it is recommended that the labeling for this product be revised as appropriate, in order to incorporate pharmacokinetic information for dobutamine. If the sponsor decides to follow

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OCPB's advice and update the labelings for Dobutrex[®] Injection, the pharmacokinetic labeling information can be based on in-house data and/or published literature. It is recommended that the following format be followed:

The "Pharmacokinetics" portion should present information for dobutamine under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be a section with the heading of *Special Populations*, where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, and Hepatic Insufficiency* should be included. After that, should be a section with the heading of *Drug-Drug Interactions*, in which available drug interaction information should be included. Finally, a *Pharmacokinetic/Pharmacodynamic* section should be presented, if such information is available. Where relevant information is lacking it should be so stated.

3. The sponsor should be informed that some of the FDA's guidances include specific recommendations for certain sections of the labeling. Examples of those guidances are: "In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling", "Pharmacokinetics in Patients with Impaired renal Function: Study design, Data Analysis, and Impact on Dosing and Labeling", Pharmacokinetics in patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (Draft Guidance), etc. These guidances are available in the FDA's web-site.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics



RD/FT Initialed by Patrick J. Marroum, Ph.D. _____

cc: NDA 17-820, HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm)

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/s/

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