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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 17-820/S-037

Administrative Documents

RHPM Review of Final Printed Labeling (FPL)

Application: NDA 17-820/SLR-037
Dobutrex Solution (Dobutamine Injection, USP)
250 mg/20 ml Vial

Applicant: Eli Lilly and Company

Document Date: August 27, 2001

Receipt Date: August 28, 2001

FPL submitted: April 30, 2002

FPL received: May 3, 2002

Type of Supplement: Geriatric Labeling Supplement

Background: Eli Lilly submitted NDA 17-820/S-037, dated August 27, 2001, received August 28, 2001, to propose under the heading of **PRECAUTIONS**, the establishment of a **Geriatric Use** subsection. The information regarding dobutamine use in the geriatric population was submitted in response to a Federal Register Notice of August 27, 1997 that amended the regulations governing the content and format of labeling for human prescription drug products to include information pertinent to the appropriate use of drugs in the elderly (persons aged 65 years and over) and to facilitate access to this information by establishing a "Geriatric Use" subsection in the labeling.

An approvable letter was issued on March 15, 2002 requesting revisions to the **Geriatric Use** subsection as well as to the **DESCRIPTION** and **HOW SUPPLIED** sections of the labeling. The sponsor submitted a response dated March 26, 2002 agreeing to the Division's revisions to the **Geriatric Use** subsection and the **DESCRIPTION** section ("molecular structure, formula, and weight should be revised to reflect Dobutamine Hydrochloride and not Dobutamine alone)." However, they stated that they would not be adding "Rx only" to the package insert as requested in the approvable letter. In a telephone conversation between Dr. Bryn Bright of Eli Lilly and myself on March 21, 2002, she explained that the removal of the "Rx only" from the package insert was being made to all Lilly products. She noted that the change was allowed by the FDA Guidance "*Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements.*" I stated this deletion was acceptable and noted that our request to put "Rx only" in the package insert was made after it appeared that it was omitted inadvertently when compared to the previously approved labeling supplement (S-036, July 29, 1998).

Review:

The sponsor submitted final printed labeling revised as follows:

1. Under **PRECAUTIONS**, a new **Geriatric Use** subsection was added that reads as follows:

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.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

2. Under **DESCRIPTION**, the molecular structure, molecular formula, and molecular weight have been revised to reflect dobutamine hydrochloride and not dobutamine alone. Note: The molecular weight is listed as 337.84 which is slightly different from the 337.85 listed in the last approved labeling supplement, S-036. Dr. Srinivasachar said that 337.84 is the correct USP molecular weight.

Comments/Recommendations: The final printed labeling submitted was in accordance with the revisions listed in the approvable letter with the exception noted on the previous page. I will draft an approval letter for Dr. Throckmorton's signature.

Edward Fromm
Regulatory Health Project Manager

dr: ef/7-11-02

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/s/

Edward Fromm
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RHPM Review of Draft Labeling

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The sponsor submitted draft labeling with the following changes:

Under **PRECAUTIONS**, a new **Geriatric Use** subsection has been established with the following wording:

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.

The biopharmaceutics reviewer thought the above language was appropriate but noted that a **Pharmacokinetic** subsection should be established under the **CLINICAL PHARMACOLOGY** section. The **Pharmacokinetic** subsection should be further expanded to include subheadings of *Absorption, Distribution, Metabolism, and Excretion*.

The medical officer said the sponsor's proposed language was acceptable but thought that the paragraph (from 21 CFR 201.57(a)(10)) that reads "In general, dose selection for an elderly patient should be cautious, usually reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy" should be inserted after the first paragraph above.

Dr. Lipicky reviewed the supplement and said the **Geriatric Use** subsection should be revised as follows:

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.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

He also thought it was unnecessary to add a **Pharmacokinetics** subsection under the **CLINICAL PHARMACOLOGY** section.

Comments/Recommendations: The wording for the new Geriatric Use subsection is consistent with 21 CFR 201.57(10). When doing a comparison of the current draft labeling with the last approved labeling change (S-036, approved July 29, 1998), I noticed the following differences:

1. Under **DESCRIPTION**, the established name, description of the chemical name, molecular formula, structure and weight are different from the last approved labeling. The sponsor refers to some of these changes in their previous annual reports, but gives little explanation for them. Dr. Srinivasachar said the USP changed, in their most recent compendium, the established name of Dobutamine Hydrochloride Injection to Dobutamine Injection, USP. Dobutamine Injection, however, is described in the compendium as the hydrochloride salt of Dobutamine. Therefore Dr. Srinivasachar suggested the following changes:

The molecular structure, formula, and weight should be revised to reflect Dobutamine Hydrochloride and not Dobutamine alone.

2. Under **HOW SUPPLIED**, the statement "Rx only" was omitted. It should be reinserted in this section or relocated to above the **DESCRIPTION** section of the labeling.

It appears that FPL was never submitted as specified in the approval letter of July 29, 1998. I will draft an approvable letter for Dr. Throckmorton's signature.



Edward Fromm
Regulatory Health Project Manager

dr: ef/2-26-02

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/s/

Edward Fromm
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