

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

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

**Medical Review(s)**



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#### Memorandum

**DATE:** January 26, 2002  
**FROM:** Shari L. Targum, M.D.  
**TO:** NDA #17-820  
**SUBJECT:** Supplement #S-037 (Geriatric Labeling Supplement)

Correspondence Date: August 27, 2001  
Date Received: August 28, 2001  
Date Assigned to Current Reviewer: August 29, 2001  
Drug Name: Dobutrex® (Dobutamine Injection, USP)  
Sponsor: Lilly

The sponsor has submitted a Geriatric labeling supplement for the this dobutamine product. This drug is currently approved (in the dosages 0.5 to 40 µg/kg/min) for short-term parenteral inotropic support in patients with cardiac decompensation due to depressed contractility resulting from organic heart disease or cardiac surgical procedures.

#### Geriatric Use

The sponsor has proposed the following labeling, under 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.”

In support of this labeling, the sponsor has submitted the following:

1. The Integrated Summary of Safety from the original submission (E.8, pages 315, 339-343). In Table E.8.B, 84 patients >60 years and 46 patients >65 years received dobutamine (out of a total of 360 patients). In pages 339-343 (overall conclusions on efficacy and safety) there is no subgroup analysis for elderly vs. younger patients in either parameter.
2. Anthopoulos LP et. al. Stress Echocardiography in Elderly Patients with Coronary Artery Disease. JACC 28 (1): 52-9, 1996. In this study of 120 patients ≥ 70 years old, all patients randomly underwent dobutamine and adenosine stress echocardiography on different days and different sequences. No blinding or control group is mentioned; therefore, this reviewer assumes that this was open-label (the echocardiograms were read by two blinded

readers). The dobutamine infusion was discontinued in 12 patients because of hypotension (8 patients), hypertension (2) and paroxysmal atrial fibrillation (2). The adenosine infusion was associated with transient AV block in 7 patients, but the infusion was terminated early in only one patient (due to flushing and headache). There is no comparison with a younger population.

3. Chenzbraun A et.al. Impact of Age on the Safety and the Hemodynamic Response Pattern During High Dose Dobutamine Echocardiography. *Echocardiography* 16 (2): 135-142, 1999. High dose dobutamine echocardiography was tested in 164 patients < 65 years, 187 patients aged 65-79 years, and 49 patients  $\geq$  80 years old. The incidence of side effects was similar in all three age groups. Age-related difference found was a lower baseline heart rate ( $p=0.01$ ), higher baseline SBP ( $p < 0.001$ ) in the  $\geq$  80 year old group and decrease in hypertensive reponse with age. In the  $\geq$  80 year old group a drop in BP was associated with an "ischemic response" (not further defined in the paper)—however, there was no increase in major clinical events in this subgroup.
4. Renard 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). This was a small study of 10 patients aged 65 years of less and 10 patients over 65 years. Of note, 4 patients over 65 developed angina during the infusion; the conclusion was that dobutamine was effective in the elderly with MI but less well tolerated.
5. Poldermans D et. al. Dobutamine-Atropine Stress Echocardiography in Elderly Patients Unable to Perform an Exercise Test. *Arch Intern Med* 154: 2681-2686, 1994. This study evaluated 179 patients, 70-90 years old, undergoing dobutamine-atropine stress test. There was no comparator group. Most frequently observed side effects were systolic hypotension ( $> 20$  mm drop in SBP from baseline) and cardiac arrhythmias. In 2 patients the test was stopped due to hypotension with bradycardia (decrease in heart rate  $> 10$  bpm). Chills caused an interruption in stress test in two patients.
6. 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* 117 (3); 649-656, 2000. This study evaluated the above stress test in 227 patients  $\geq$  70 years old and included a matched control group of 227 patients  $< 70$  years (mean age 55). In this study there was a higher prevalence of SVT (7% vs. 1%,  $p < 0.005$ ), PVC (74% vs. 32%,  $p < 0.005$ ) during the test in the elderly vs. younger population, respectively. There was also a higher prevalence of VT (5% vs. 2%) and AF (3% vs. 0.4%) in the elderly vs. younger groups.
7. Poldermans D et.al. Cardiac Chronotropic Responsiveness to Beta-Adrenoceptor Stimulation Is Not Reduced in the Elderly. This study evaluated 360 patients of which 112 (31%) were  $> 70$  years old. There was no difference in plasma concentrations in a subgroup  $\leq 60$  years ( $n=20$ ) and  $> 60$  years old ( $n=14$ ). This study found no incidence of reduced beta-receptor sensitivity to dobutamine in elderly subjects. In the elderly with previous MI, angina, or smoking history, a reduced/unchanged HR response to dobutamine was seen despite a diminished increase in SBP. There was no discussion of early termination or side effects in this paper.

### **Comments:**

1. The numbers of patients (1893 total patients, 930 aged 65 and older) are represented in the above 7 references.
2. References #3, 4 and 6 suggest that there may be differences in either hemodynamic response or safety in the elderly compared with younger age groups. Reference #4 (Renard) was a fairly small study for conclusions to be drawn. Taken as a total, however, these references then do not support the contention that "no differences in responses" have been observed between

elderly and younger patients. However, this reviewer cannot say whether these differences (e.g., increase in cardiac arrhythmias) are due to concomitant disease or drug therapy, or decreased renal function. This issue would likely be resolved by adding the standard language that "dose selection in the elderly should be cautious..." (see Recommendations, below). It should also be noted that labeling for dobutamine already contains a warning for ectopic activity.

3. This reviewer also conducted a literature search and was unable to find any relevant additional information.

**Recommend:**

1. This reviewer suggests the following labeling, under 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.

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.

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.

2. Since no distinction is made in the literature between manufacturers, it is suggested that this labeling be generalized to the class of dobutamine.

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Shari L. Targum, MD  
Medical Officer

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date

c.c.: #17-820  
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**This is a representation of an electronic record that was signed electronically and  
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MEDICAL OFFICER