CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 17820/S036

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-820/S-036

JUL 29 1998

Lilly Research Laboratories
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your April 21, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doubtrex (dobutamine HCl) Injection 12.5 mg/ml.

We acknowledge receipt of your submission dated July 23, 1998.

This supplemental new drug application provides for draft labeling revised to add information relating to the dosing of these products in the pediatric population as required in the December 13, 1994 Federal Register notice entitled: "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' subsection in the Labeling" and, as amended, to update the **INDICATIONS AND USAGE** section by providing the most recent dosing recommendations for the use of intravenous inotropic compounds.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling included in your July 23, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling included in your July 23, 1998 submission. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-820/S-036." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

/S/ 7/29/98

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 17-820
HFD-110/Div. Files
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE
HFD-110/G.Buehler/7/16/98;7/16/98
sb/7/16/98;7/24/98
Initialed by: S Zimmerman/7/17/98
K Srinivasachar/7/20/98
P Gill-Kumar
C Resnick/7/21/98
R Fenichel/7/21/98
G Buehler for N Morgenstern
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APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 17820/S036

ADMINISTRATIVE DOCUMENTS

JUL 29 1998

RHPM REVIEW OF LABELING

NDA 17-820/S-036 Dobutrex (dobutamine HCl) Injection

Sponsor: Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Date of Submission: April 21, 1998

BACKGROUND

This supplemental application was a resubmission of the application submitted on December 12, 1996 in response to the December 13 1994 Federal Register notice requesting revised labeling to address pediatric use. The original application requested a change in the INDICATIONS AND USAGE section of the labeling by adding "pediatric patients" to the existing language in that section. The firm was informed that the material submitted would not support a pediatric indication for Dobutrex. Lilly indicated that they would amend their application. Numerous delays were encountered in revising the application. The firm stated that they wanted to wait for the rumored new regulations governing pediatric submissions before revising the application. The initial application was eventually withdrawn and a new application submitted on April 21, 1998

The submission was reviewed by Dr. Fenichel. He drafted revised labeling for the proposed pediatric revisions. These revisions were sent to Dr. Lipicky for review. Dr. Lipicky noted his changes on Dr. Fenichel's review (appended to this review). A labeling draft was prepared and forwarded to Lilly. The firm proposed the following minor revisions that were acceptable to the Agency:

1. The second paragraph under **CLINICAL PHARMACOLOGY** was deleted because it was considered redundant with the statement under **PRECAUTIONS, Pediatric Use.** The parenthetical statement, See Pediatric Use under Precautions, was added to the end of the first paragraph.

2. The second paragraph under **INDICATIONS AND USAGE** was moved to the **WARNINGS, Increase in Heart Rate or Blood pressure** section as the next to the last sentence.

3. Under **DOSAGE AND ADMINISTRATION, Recommended Dosage,** the sentence,"On rare occasions infusion rates up to 40 ug/kg/min have been required to obtain the desired effect," was retained.

4. The last statement under **ADVERSE REACTIONS** relating to longer-term safety was deleted.

5. Certain statements throughout the labeling describing clinical experience with Dobutrex were qualified with "in adults" to indicate that the experience was not necessarily in pediatric patients.

On April 24, 1998 a supplement request issued to this NDA requesting revised labeling to address the recommendations made at the January 1998 Advisory Committee meeting relating to the labeling of intravenous inotropic compounds. Lilly wanted to incorporate the requested changes into the labeling draft for S-036. The firm was advised to amend the application with the requested text from the April 24, 1998 letter and submit it with the agreed revisions relating to pediatric dosing. The supplemental application could then be approved for both changes. Draft labeling was submitted on July 23, 1998 containing the the agreed upon pediatric revisions in addition to the requested Advisory Committee revisions.

REVIEW

The submitted draft was reviewed and found to be acceptable. An approval on draft labeling letter will be prepared for Dr. Lipicky's signature.

/S/ 7/27/98
Gary Buehler
Project Manager

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
HF-2 MEDWATCH

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

/S/

Date: 25 June 1998
From: Robert R. Fenichel, HFD-110
Subject: pediatric labeling for dobutamine (DOBUTREX®, Lilly), NDA 17-820)
To: Raymond J. Lipicky, HFD-110

In a supplement submitted on 21 April, Lilly proposes that the labeling of dobutamine be changed to indicate what is known about the use of dobutamine in pediatrics. This supplement is little more than a revised cover letter to the supplement that was received on 12 December 1996, with minor changes in the wording of the proposed revisions to the label.

The pediatric-labeling issues raised here are complicated by the fact that dobutamine is a good example of a Pharmacologic Tool, as the Division has come to use that phrase. The **Indications and Usage** section of the current approved labeling reads in pertinent part that

> DOBUTREX SOLUTION is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

That is, the benefits of dobutamine have historically been defined in terms of hemodynamic parameters, and not in terms of survival or symptomatic relief. It is a matter of common knowledge that dobutamine is widely used for its hemodynamic effects in many patients who have neither organic heart disease or a history of cardiac surgery.

Lilly has done no new studies, but the supplement includes copies of 28 papers[1-28] from the published literature, describing studies that involved a total of about 654 patients.* In the original cover letter, Lilly described the means by which these 28 studies were selected:

> Major online pharmaceutical databases for references to dobutamine and pediatric use were searched using dobutamine as the descriptor. The initial search retrieved 439 items which were reduced by utilization of the Derwent Drug File. Derwent indexing links the drug term to the pediatric term, thereby reducing the incidence of false drops due to terms which are valid but unrelated.

I have not attempted to replicate or second-guess this selection process, so the remainder of this memo relies upon the assumption that Lilly's selection of papers was comprehensive. Some confidence in Lilly's selection is provided by the fact that Lilly missed none of the primary sources cited in a relatively recent review article.[29]

* I say "about" because some authors contributed to two or more of the 28 papers, and internal evidence suggests that up to 10% or so of the patients may have been double-counted.

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Not all of the studied patients had organic heart disease or were recovering from cardiac surgery. Other diagnoses included sepsis, meconium aspiration, near-drowning, trauma, respiratory distress syndrome, and nonspecific hypotension associated with prematurity. Some of the reported data comes from healthy pediatric subjects. From the submitted papers, it is not possible to classify responses to dobutamine by diagnosis, or even to provide a table showing how many patients there were with each of the diagnoses listed.

Only about half of the studied patients participated in randomized studies,[6,7,9,16,21,22,28] and only about 102 of them participated in the three studies[6,16,21] that were randomized and blinded. Nine of the studies[4,7,10,13,15,17,22,25,26] were described only in abstracts. About 250 of the studied patients were neonates, with the rest of various ages up to 22 years.

Pharmacokinetics

Eight of the reported studies[2-4,10,11,17,18,24] provided pharmacokinetic data, but only two studies[4,24] provided any data other than total body clearance. The reported clearance rates ranged from 11 to 527 mL/min/kg, and variability was nearly as great within studies as across them. One group[11] found that clearance tended to decline as a function of age, but most of the others explicitly denied perceiving any such relationship.

The volume of distribution of dobutamine was estimated at 1.1[24] and 3.2[4] L/kg; these studies excluded neonates. The same two studies provided estimates of a monoexponential half-life of 3.9 minutes[4] and biexponential half-lives of 1.65 and 25.8 minutes.[24]

These data may seem scanty, but they are comprehensive compared to what is available in the current (adult) label. The entire pharmacokinetic content of the current label is

> The onset of action of DOBUTREX SOLUTION is within 1 to 2 minutes; however, as much as 10 minutes may be required to obtain the peak effect of a particular infusion rate.
>
> The plasma half-life of dobutamine hydrochloride in humans is 2 minutes.

Thus, the available data are consistent with Lilly's proposed claim that the pharmacokinetics of dobutamine are similar in adult and pediatric patients, but the available data are consistent with almost any claim at all.

Two of the reported studies[12,28] studied a single infusion rate each (2.5 and 10 µg/kg/min); two others[23,27] nonrandomly assigned patients to either 7.5 or 10 µg/kg/min; and one trial[7] was a randomized three-way cross-over using doses of 2.5, 5, and 10 µg/kg/min. The remaining 23 trials were about evenly split between forced-titration designs and designs in which the infusion was titrated *ad lib* at the discretion of the investigator. The infusion rates used in the

multi-rate trials ranged from 0.5 to 30 μg/kg/min, but only 61 patients were reported to have been exposed to rates less than 2 μg/kg/min, and only 40 patients were reported to have been exposed to rates greater than 20 μg/kg/min.

Pharmacodynamics

Most of the reported studies were nonrandomized trials in which dobutamine was titrated in open-label fashion in order to improve the hemodynamics of critically-ill children. The objective in most of these settings was to achieve a perfusing systemic blood pressure without inducing dysfunctional tachycardia.

In several of these studies,[2,3,10,11,17,18] serum concentrations of dobutamine were measured, and the investigators estimated the threshhold levels of dobutamine above which changes could be detected in cardiac output (CO), systemic blood pressure (BP), and heart rate (HR). These estimates were generally made by using linear approximations to the midportion of the dose-response curve. More or less consistently, the estimated threshholds follow the pattern $CO < BP \ll HR$; the weighted-average values were 24, 28, and 58 ng/ml, respectively. This pattern is consistent with the overall hemodynamic results achieved: The weighted-average changes ranged from a 32% increase in CO down to a 9% increase in HR.

Eleven studies[7,9,12,16-19,21,25-27] were performed in neonates, and most of these were open only to premature infants. In several of these studies, dobutamine was compared to dopamine. For a given change in heart rate or at maximal effect, the blood-pressure response to dobutamine was consistently[7,9,12,16,21] inferior to that associated with dopamine. In the randomized, double-blind study[21] by Rozé *et al.*, dobutamine provided a greater increase in cardiac output than dopamine, but a lesser improvement in mean arterial pressure. In a study[19] in which dobutamine was administered to infants who were failing to respond to dopamine, there was no evidence of an incremental additive effect.

As was the case with respect to pharmacokinetics, there were no consistent trends of variation in effect with age.

Sponsor's Proposed Labeling Changes

Lilly's proposed labeling includes scattered changes to bring the labeling into cosmetic compliance with current standards: [ ] replaces [ ] and so forth. These changes do not constitute a serious effort to bring modern structure to this ancient, ugly label. In addition, Lilly proposes substantive changes as follows:

L1. Under **Clinical Pharmacology**, Lilly would add

[ ]

L2. In the Pediatric Use subsection of **Precautions**, Lilly would replace

with

L3. Under **Dosage and Administration**, Lilly would add

L4. Also in **Dosage and Administration**, Lilly proposes to add some lines to a table (their Table 1) that shows the necessary IV infusion rate (in mL/min) to achieve various drug-delivery rates (in µg/min) with various concentrations of dobutamine. Confusingly, this table's rows and entries are wrongly identified as showing values in µg/kg/min and mL/kg/min, respectively.

L5. Also in **Dosage and Administration**, Lilly proposes to add some lines to a table (their Table 2) that shows the necessary IV infusion rates (in mL/h) to achieve various drug-delivery rates (in µg/kg/min) for patients of various weights and solutions containing various concentrations of dobutamine.

Conclusions

Dobutamine has never been approved as more than a pharmacologic tool.

At least in pediatric patients, dobutamine appears to exhibit huge inter-patient variation in pharmacokinetics. No important determinants of this varia-

tion (*e.g.*, drug interactions, phenotypic variation in enzyme activity, and so on) seem to have been identified.

The reported use of dobutamine now extends from neonatal premature infants to elderly adults, with roughly similar infusion rates used across age groups. Dobutamine is typically titrated to achieve hemodynamic effect; most investigators have reported final infusion rates in the range of 2–20 µg/kg/min, but there are scattered reports of successful use at rates slightly outside these limits.

Clinicians caring for neonates and infants consistently report that (patient-specific) infusion rates of dobutamine can frequently be found to yield increases in cardiac output and systemic blood pressure without substantial increases in heart rate. In the few studies that compared dobutamine to dopamine in the treatment of premature neonates, however, dobutamine was consistently inferior to dopamine in its ability to raise systemic pressure while avoiding tachycardia. In a very small study (N=12) in neonates who had inadequate responses to dopamine, the addition of dobutamine did not result in additional improvement of hemodynamics.

Recommendations

Lilly's proposal **L1** should not be accepted. It may be true that plasma concentrations and clearance rates are similar after equivalent infusions in adults and children, but we are not in any position to say that this is so. We have, after all, no information whatsoever regarding the adult values, and the pediatric clearance values are uselessly variable.

Instead, I would add to the **Clinical Pharmacology** section language like the following:

Lilly's proposal **L2** should be reworded as follows:

In particular, the speculation as to mechanism, and the references to other sections, are unnecessary.

Lilly's proposal **L3** might be acceptable, but the addition of this separate paragraph implies that the adult & pediatric dosing recommendations are really different. The current (adult) dosing recommendation is

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* Their past tense makes them sound more like reports than recommendations, but that is easy to fix.

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