N18-826/S-027

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-826/S-027

Abbott Laboratories
Attention: Mr. Kenneth Oh
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Dear Mr. Oh:

Please refer to your October 11, 2000 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dopamine Hydrochloride in 5% Dextrose Injection in Flexible Container.

We note that this supplement was submitted as a "Special Supplement – Changes Being Effected" under 21 CFR 314.70(c).

This supplemental new drug application provides for final printed labeling revised as follows:

1. Under **Description,** the last paragraph has been changed to:

   The flexible plastic container is fabricated from a specially formulated CR3 plastic material. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components form the plastic in very small amounts; however; biological testing was supportive of the safety for the plastic container materials. Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period.

2. The package insert, overwrap and container labeling have been revised to emphasize visually the dopamine name. In addition to the changed design and look of the labeling, the container and overwrap labeling have been revised as follows:

   (a). The statement[ ] has been replaced with "For I.V. Use. Usual Dosage: See Insert."
   (b). The statement[ ] has been replaced with the "Rx Only" symbol.

We also note that there were several minor changes to the container labeling.

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 submitted final printed labeling (package insert, container, and carton labels. Accordingly, the supplemental application is approved effective on the date of this letter.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

4/10/01

{See appended electronic signature page}

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

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
December 14, 2000	February 23, 2001	01-0002

TO: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Edward From, Project Manager
HFD-110

PRODUCT NAME:	MANUFACTURER:
Dopamine Hydrochloride in 5% Dextrose Injection, USP 200 mg/250 mL, 400 mg/250 mL, 400 mg/500 mL, 800 mg/250 mL and 800 mg/500 mL **NDA #: 18-826/SL-027**	Abbott Laboratories

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA reviewed the proposed container labels, overwrap labeling, and package insert labeling of Dopamine for possible interventions that may help minimize medication errors.

OPDRA RECOMMENDATION: OPDRA recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined in the review in order to further minimize the potential for medication errors detected through our post-marketing surveillance. We also recommend that all manufactures of Dopamine be requested to implement the same labeling revisions.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Post-Marketing Safety Review
(Container Labels and Package Insert Labeling)

DATE OF REVIEW: **February 6, 2000**

NDA: **18-826/SL-027**

NAME OF DRUG: **Dopamine Hydrochloride in 5% Dextrose Injection, USP**

NDA HOLDER: **Abbott Laboratories, Inc.**

I. EXECUTIVE SUMMARY

Abbott Laboratories submitted a supplement to revise the labels and labeling of Dopamine Hydrochloride in 5% Dextrose Injection, USP in response to customer needs and to standardize their label design. The sponsor states the "label design is more visually distinctive and is intended to improve patient safety by minimizing product mix-ups". The Division of Cardio-Renal Drug Products (HFD-110) forwarded the container labels, product overwrap and package insert labeling to OPDRA for review and comment. In conjunction with the labeling review, OPDRA conducted a post-marketing review to determine the extent of product confusion in the marketplace. Eight (8) case reports were retrieved from the AERS and DQRS databases that involved confusion between different strengths of the same product and/or administration of the wrong drug due to the similar packaging and labeling designs of dopamine and dobutamine. However, this confusion is not isolated to Abbott's Dopamine/Dobutamine product line. Several of the case reports involved other manufacturers as well. OPDRA believes the proposed labeling interventions will help minimize the risk of medication errors between Dopamine and Dobutamine. However, we have provided additional labeling recommendations in order to address the additional problems that we have identified through post-marketing surveillance.

The sponsor has also submitted a supplement for Dobutamine in 5% Dextrose Injection with similar labeling revisions. The Dobutamine labels and labeling are addressed separately in OPDRA consult (01-0003).

II. RISK ASSESSMENT

A. OPDRA searched MEDLINE for published reports of medication errors occurring with Dopamine and/or Dobutamine, using the MeSH headings "Medical Errors" and "Medication Errors" to narrow the focus of the search. This search strategy uncovered three published reports, two of which, attributed medication errors to the similarity of the labeling of dopamine vials rather than confusion with the pre-mixed bags. Neither of which involved vials that were manufactured by Abbott. The third report involved an inappropriate therapeutic intervention that led to a massive overdose of Dobutamine.

B. OPDRA also searched the FDA Adverse Event Reporting System *(AERS)* database for all post-marketing safety reports of medication errors reported for the active ingredient terms "dopamine%" and "dobutamine%", using the Meddra Preferred Term, DRUG MALADMINISTRATION. In addition, the Drug Quality Reporting System *(DQRS)* database was searched for similar reports with dopamine and dobutamine. This search strategy retrieved eight medication error reports specifically relating to confusion with dopamine and/or dobutamine. The case reports are summarized in Table 1 (see attachment A). Reports not relating to product confusion were discarded and not included in the review. Four of the reported cases involved Baxter's product line, two cases involved Abbott's product line, and the remaining reports did not identify a manufacturer.

One of the two case reports involving Abbott's product line was an actual error that resulted in an under dose of Dopamine. The patient required intervention and treatment with levophed. The most serious case reported involved Baxter's product line. A patient was being coded for cardiac arrest and the nurse administered Dobutamine rather than Dopamine. The patient outcome in this case is unknown. However, the same reporter stated the similar labeling and packaging of these drug products caused confusion and near miss errors on several occasions. Other reports describe the similar events of ICU nurses administering the wrong drug or strength due to similar product labeling.

C. SAFETY EVALUATOR RISK ASSESSMENT

The major revisions to the Abbott Dopamine label are the stylized type and font size and color of this established name (DOPamine), the expression of strength, and location of strength. The packaging configurations effected by these revisions include 0.08% - 250 mL and 500 mL pre-mixed bags, 0.16% - 250 mL and 500 mL pre-mixed bags, and 0.32% - 250 mL pre-mixed bags.

The currently marketed container label display appears as follows:

400 mg DOPAMINE HCl in 5% Dextrose Injection, USP

1600 mcg/mL
micrograms/mL

The revised container label display appears as follows:

800 mcg/mL micrograms/mL
DOPamine HCl in 5% Dextrose Injection, USP 400 mg Total

OPDRA believes the proposed labeling revisions will help to differentiate Dopamine from Dobutamine. However, the proposed revisions will not eliminate the problem regarding product strength confusion that has been reported post-marketing with these drug products.

OPDRA completed a side-by-side comparative review of the new labels and labeling and conclude that the bags remain extremely similar in appearance. The pre-mixed bags are available in three different strengths (200 mg, 400 mg and 800 mg). However, the concentration expressed as "mcg/mL" can be the same dependent on the fill volume. For example, the concentration of "mcg/mL" for the 200 mg/250 mL and 400 mg/500 mL is expressed as 800 mcg/mL and are not differentiated by boxing, contrasting color or any other means. Several of the post-marketing reports describe the administration of sub-therapeutic or supra-therapeutic doses of dopamine due to nurses selecting the wrong concentration because of the similar appearance of these bags.

OPDRA believes other interventions can be initiated to further differentiate the product names and the labels and labeling of these two products. For example:

- We acknowledge the sponsor's effort to differentiate the established name with the use of capital letters for the prefix of the name (DOPamine). However, OPDRA believes it is imperative to increase the prominence of this portion of the established name in order to successfully distinguish this product from Dobutamine.

- In a side-by-side comparison the bags appear extremely similar in appearance to one another despite the numerous interventions that have already been proposed. The pre-mixed bags are available in three different strengths (200 mg, 400 mg and 800 mg). However, the concentration expressed as "mcg/mL" can be the same dependent on the fill volume. For example, the concentration of "mcg/mL" for the

200 mg/250 mL and 400 mg/500 mL is expressed as 800 mcg/mL and is the first item seen on the label. The total milligram amount appears following the established name. Neither expression of strength is differentiated in any manner. Post-marketing reports have demonstrated confusion with regard to selection of the wrong product strength because of the similarity in appearance and color of the bags. OPDRA believes the probability for the recurrence of these types of errors is high with the current label design. Therefore, we recommend relocating the total volume so it appears in conjunction with the total mg amount (400 mg/500 mL) and request this expression of strength be differentiated with the use of boxing, contrasting colors or some other means.

In addition, the Orange Book references eleven different companies that manufacture Dopamine. Faulding is the only sponsor to utilize a proprietary name (Intropin). The case summaries portray the confusion between Dopamine and Dobutamine as a global problem affecting several manufacturers. Therefore, we recommend that all dopamine and dobutamine labels and labeling be revised to incorporate the same stylized nomenclature. Five of the applications for Dopamine involve an abbreviated new drug application (ANDA). Therefore, OPDRA contacted the Office of Generic Drugs regarding this issue and they have agreed to request the generic manufacturers to implement the same labeling revisions at the time of next printing.

III. COMMENTS TO BE PROVIDED TO THE SPONSOR:

A. GENERAL COMMENT

We acknowledge your efforts to differentiate the established name with the use of capital letters for the prefix of the name (**DOP**amine). However, OPDRA believes it is imperative to increase the prominence of this portion of the established name in order to successfully distinguish this product from Dobutamine. We recommend further differentiating "DOP" with the use of a contrasting color on ***all*** labels and labeling. (i.e., **DOP**amine).

B. CONTAINER LABEL (200 mg/250 mL, 400 mg/500 mL, 400 mg/250 mL, 800 mg/500 mL, and 800 mg/250 mL)

1. See GENERAL COMMENT.

2. Delete the statement "micrograms/mL" that appears following "XXX mcg/mL". It is unnecessary and adds unwanted clutter to the label.

3. In a side-by-side comparison the bags appear extremely similar in appearance to one another despite the numerous interventions that have already been proposed. The pre-mixed bags are available in three different strengths (200 mg, 400 mg and 800 mg). However, the concentration expressed as "mcg/mL" can be the same dependent on the fill volume. The concentration of "mcg/mL" for the 200 mg/250 mL and 400 mg/500 mL is expressed as 800 mcg/mL and is the first item seen on the label. For example:

250 mL

800 mcg/mL micrograms/mL
DOPamine HCl in 5% Dextrose Injection, USP **200 mg Total**

500 mL

800 mcg/mL micrograms/mL
DOPamine HCl in 5% Dextrose Injection, USP **400 mg Total**

The total milligram amount appears following the established name and is not differentiated in any manner. Post-marketing reports have demonstrated confusion with regard to selection of the wrong product strength because of the similarity in appearance and color of the bags. OPDRA believes the probability for the recurrence of these types of errors is high with the current label design. Therefore, we recommend relocating the total volume so it appears in conjunction with the total mg amount (400 mg/500 mL) and request this expression of strength be differentiated with the use of boxing, contrasting colors or some other means. For example:

800 mcg/mL
DOPamine HCl in 5% Dextrose Injection, USP **200 mg/250 mL**

800 mcg/mL
DOPamine HCl in 5% Dextrose Injection, USP **400 mg/500 mL**

C. OVERWRAP LABELING (200 mg/250 mL, 400 mg/500 mL, 400 mg/250 mL, 800 mg/500 mL, and 800 mg/250 mL)

1. See GENERAL COMMENT and comments under CONTAINER LABEL.

2. We note your attempts to differentiate the product strengths on the overwrap with the use of color. However, the bags still appear very similar when compared side by side. The "1600 mcg/mL" on both the 400 mg/250 mL and 800 mg/500 mL appear in a solid red background. We recommend differentiating the strengths on the overwrap in the same manner as the bag itself.

IV. RECOMMENDATIONS

OPDRA recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined above in order to further minimize the potential for medication errors detected through our post-marketing surveillance.

We also recommend that all manufactures of Dopamine be requested to implement the same labeling revisions.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-0915.

/S/ 2/23/01

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 2/23/01

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

ATTACHMENT A

TABLE I

1993 IL 43	1522232 (H 3007311 AO)	Abbott	Dopamine 800 mg	Dopamine 200 mg	Pt under dosed. Blood pressure decreased to 76/48 (baseline 110/80). The reaction was treated with Levophed.
2000 FL Unknown	3474547-9 (USP 52909)	Abbott	Dobutamine 250 mg/250 mL	Dobutamine 500 mg/250 mL	Error on the part of the wholesaler. The pharmacy ordered 250 mg/250 Ml but received both strengths. The pharmacy technician caught the error and did not place the 500 mg bags into stock.
1995 Unknown	USP 080386	Unknown	Dobutamine	Dopamine	The pharmacist placed Dopamine in the bag of admixture labeled Dobutamine. No patient injury.
1997 MO Unknown	1991596	Unknown	Dobutamine	Dopamine	3 times in last two years, a nurse in ICU hung the wrong drug due to the similarity of product packaging. No patient injury.
2000 TX 83	3459079-6	Baxter	Dopamine	Dobutamine	Life-threatening. The patient was being coded for cardiac arrest and the nurse grabbed Dobutamine because of the similar outer wrapping. Both of the drugs start with the same letters and are printed in red. This has caused confusion and near miss errors on several occasions.
1999 OR	3309923-8	Baxter	Dobutamine 1000 mg/250 mL	Dobutamine 500 mg/250 mL	Product labeling for Dobutamine is similar. Both are labeled with red print with only difference being the strength. Subsequently ICU nurses have pulled the wrong product leading to sub or supratherapeutic dosing.
1999 ISMP	3283683-1 (USP 52390)	Baxter	Dobutamine 500 mg/250 mL	Dobutamine 1000 mg/250 mL	The bags look exactly the same in size and silver color with blue print on whit labels. The potential for error exists.
2000 AZ	3568825-2	Baxter	Dopamine	Lidocaine	Both medications are labeled in red lettering of similar or same font size and spacing on the upper half of the IV bags.