CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20255/S6

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-255/S-006

JUN 14 2000

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 and Wilson Road, RLT-10
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your March 21, 1999 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dobutamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207.

We acknowledge receipt of your submission dated April 27, 2000, which constituted a complete response to our June 16, 1999 approvable letter.

This supplemental new drug application provides for final printed labeling revised to include pediatric-related changes to the **CLINICAL PHARMACOLOGY, INDICATIONS and USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE and ADMINISTRATION** sections of the 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 included with your April 27, 2000 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

Sincerely,

/S/ 6/14/06

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20255/S6

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

1999

NDA 20-255/S-006

Baxter Healthcare Corporation
Attention: Ms. Marcia Marconi
Route 120 & Wilson Road; RLT-10
Round Lake, IL 60073

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated March 12, 1999, received March 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dobutamine Hydrochloride in 5% Dextrose Injection in Plastic Container.

This supplemental application provides for draft labeling revised to include information on the dosing of this product in the pediatric population.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

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

Sincerely yours,

/S/ 4/26/99

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 20-255
HFD-110/Div. Files
HFD-95/DDMS
DISTRICT OFFICE
HFD-110/G.Buehler/4/22/99;4/27/99
sb/4/23/99;4/30/99
Initialed by: S Zimmerman/4/27/99
K Srinivasachar/4/27/99
C Ganley for K Knudsen/4/18/99
Z McDonald for N Morgenstern
filename: 20255s006ae.doc

APPROVABLE (AE)

/S/
4/30/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20255/S6

FINAL PRINTED LABELING

*BAR CODE POSITION ONLY

071904854

APPROVED
JUN 14 2000

7-19-4-854

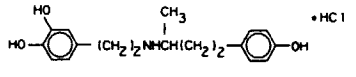
Baxter

Dobutamine Hydrochloride in 5% Dextrose Injection

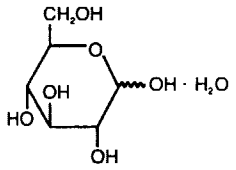
in Plastic Container
Viaflex® Plus Container

Description

Dobutamine Hydrochloride in 5% Dextrose Injection is a sterile, nonpyrogenic solution of Dobutamine Hydrochloride, USP and Dextrose, USP in Water for Injection, USP. Dobutamine hydrochloride is chemically designated as (±)-4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride. It is a synthetic catecholamine. Dextrose Hydrous, USP is chemically designated as D-Glucopyranose monohydrate. Structural formulas are shown below:



Dobutamine Hydrochloride, USP



(D-Glucopyranose monohydrate)
Dextrose Hydrous, USP

Dobutamine Hydrochloride in 5% Dextrose Injection is intended for intravenous use only. It contains no antimicrobial agents. The pH is adjusted with sodium hydroxide and/or hydrochloric acid. Sodium bisulfite is added as a stabilizer. The solution is intended for single use only. When smaller doses are required, the unused portion should be discarded. Composition, osmolarity, pH and caloric content are given in Table 1.

Table 1

Composition†
Dobutamine Hydrochloride
in 5% Dextrose Injection

Dobutamine (mg/Container)	Dobutamine (mcg/mL)	Dextrose Hydrous, USP (g/L)	Osmolarity (mOsmol/L) (calc) *	pH	kcal/L
250 mg/500 mL	500	50	256	3.5	170
250 mg/250 mL	1000	50	259	(2.5 to 5.5)	170
500 mg/500 mL	1000	50	259	3.5	170
500 mg/250 mL	2000	50	266	(2.5 to 5.5)	170
1000 mg/250 mL	4000	50	280	3.5 (2.5 to 5.5)	170

*Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L. Administration of substantially hypertonic solutions (≥ 600 mOsmol/L) may cause vein damage.
†Approximately 5 mEq/L sodium bisulfite is added as a stabilizer.

This Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 2207 Plastic). Viaflex® containers, including Viaflex® Plus containers, are made of flexible plastic and are for parenteral use. Viaflex® Plus on the container indicates the presence of a drug additive in a drug vehicle. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Clinical Pharmacology

Dobutamine hydrochloride is a direct-acting inotropic agent whose primary activity results from stimulation of the ß-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term - not more than several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of dobutamine is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

The effective infusion rate of dobutamine varies widely from patient to patient, and titration is always necessary (*see* **Dosage and Administration**). At least in pediatric patients, dobutamine-induced increases in cardiac output and systemic pressure are generally seen, in any given patient, at lower infusion rates than those that cause substantial tachycardia (*see* **Pediatric Use** under **Precautions**).

Dextrose provides a source of calories. Dextrose is readily metabolized, may decrease losses of body protein and nitrogen, promotes glycogen deposition and decreases or prevents ketosis if sufficient doses are provided.

Indications and Usage

Dobutamine in 5% Dextrose Injection is 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. Experience with intravenous dobutamine in controlled trials does not extend beyond 48 hours of repeated boluses and/or continuous infusions.

Whether given orally, continuously intravenously, or intermittently intravenously, neither dobutamine nor any other cyclic-AMP-dependent inotrope has been shown in controlled trials to be safe or effective in the long-term treatment of congestive heart failure. In controlled trials of chronic oral therapy with various such agents, symptoms were not consistently alleviated, and the cyclic-AMP-dependent inotropes were consistently associated with increased risks of hospitalization and death. Patients with NYHA Class IV symptoms appeared to be at particular risk.

Contraindications

Dobutamine Hydrochloride in 5% Dextrose Injection is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

Warnings

Increase in Heart Rate or Blood Pressure

Dobutamine Hydrochloride in 5% Dextrose Injection may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of adult patients in clinical studies have had rate increases

of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutamine in D_5W.

Ectopic Activity

Dobutamine Hydrochloride in 5% Dextrose Injection may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Hypersensitivity

Reactions suggestive of hypersensitivity associated with administration of dobutamine including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

Dobutamine Hydrochloride in 5% Dextrose Injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Solutions containing dextrose should not be administered through the same administration set as blood, as this may result in pseudoagglutination or hemolysis.

The intravenous administration of solutions may cause fluid overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration of the injections.

Excess administration of potassium-free solutions may result in significant hypokalemia.

Precautions

General

During the administration of Dobutamine Hydrochloride in 5% Dextrose Injection, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of dobutamine.

Hypovolemia should be corrected with suitable volume expanders before treatment with dobutamine is instituted.

Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Do not administer unless solution is clear and seal is intact.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Usage Following Acute Myocardial Infarction

Clinical experience with dobutamine following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Drug Interactions

There was no evidence of drug interactions in clinical studies in which dobutamine was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the carcinogenic or mutagenic potential of dobutamine or the potential of the drug to affect fertility adversely have not been performed.

Pregnancy

Pregnancy Category B:

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to dobutamine. The drug, however, has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use

Dobutamine has been shown to increase cardiac output and systemic pressure in pediatric patients of every age group. In premature neonates, however, dobutamine is less effective than dopamine in raising systemic blood pressure without causing undue tachycardia, and dobutamine has not been shown to provide any added benefit when given to such infants already receiving optimal infusions of dopamine.

Adverse Reactions

Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity

A 10 to 20-mm Hg increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients (see **Warnings** regarding exaggerated chronotropic and pressor effects). Approximately 5% of adult patients have had increased premature ventricular beats during infusions. These effects are dose related.

Hypotension

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values. In rare cases, however, intervention may be required and reversibility may not be immediate.

Reactions at Sites of Intravenous Infusion

Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration.

Miscellaneous Uncommon Effects

The following adverse effects have been reported in 1% to 3% of adult patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

Administration of dobutamine, like other catecholamines, has been associated with decreases in serum potassium concentrations, rarely to hypokalemic values.

Overdosage

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.

Signs and Symptoms

Toxicity from dobutamine is usually due to excessive cardiac ß-receptor stimulation. The duration of action of dobutamine is generally short ($T_{1/2}$ = two minutes) because it is rapidly metabolized by catechol-O-methyltransferase. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, and anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of dobutamine on the myocardium may cause hypertension, tachyarrhythmias, myocardial ischemia, and ventricular fibrillation. Hypotension may result from vasodilation.

If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

The initial actions to be taken in a dobutamine overdose are discontinuing administration, establishing an airway, and ensuring oxygenation and ventilation. Resuscitative measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lidocaine. Hypertension usually responds to a reduction in dose or discontinuation of therapy.

Protect the patient's airway and support ventilation and perfusion. If needed, meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine.

Dosage and Administration

Recommended Dosage

Dobutamine Hydrochloride in 5% Dextrose Injection is administered intravenously through a suitable intravenous catheter or needle. A calibrated electronic infusion device is recommended for controlling the rate of flow in mL/hour or drops/minute.

Infusion of dobutamine should be started at a low rate (0.5-1.0 µg/kg/min) and titrated at intervals of a few minutes, guided by the patient's response, including systemic blood pressure, urine flow, frequency of ectopic activity, heart rate, and (whenever possible) measurements of cardiac output, central venous pressure,

and/or pulmonary capillary wedge pressure. In reported trials, the optimal infusion rates have varied from patient to patient, usually 2-20 µg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 µg/kg/min have been required to obtain the desired effect.

Rates of Infusion in mL/hour for dobutamine hydrochloride concentrations of 500, 1,000, 2,000 and 4,000 mg/L are in Table 2.

This container system may be inappropriate for the dosage requirements of pediatric patients under 30 kg. Other dosage forms may be more appropriate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Dobutamine Hydrochloride in 5% Dextrose Injection solutions may exhibit a pink color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency.

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Do not add supplementary medications to Dobutamine Hydrochloride in 5% Dextrose Injection. Do not administer Dobutamine Hydrochloride in 5% Dextrose Injection simultaneously with solutions containing sodium bicarbonate or strong alkaline solutions.

How Supplied

Dobutamine Hydrochloride in 5% Dextrose Injection in Viaflex® Plus plastic containers is available as follows:

2B0791	Dobutamine 250 mg/250 mL	NDC 0338-1073-02
2B0792	Dobutamine 500 mg/250 mL	NDC 0338-1075-02
2B0793	Dobutamine 1000 mg/250 mL	NDC 0338-1077-02
2B0795	Dobutamine 250 mg/500 mL	NDC 0338-1071-03
2B0796	Dobutamine 500 mg/500 mL	NDC 0338-1073-03

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended the product be stored at room temperature (25°C); brief exposure up to 40°C does not adversely affect the product.

Directions for use of Viaflex® Plus Plastic Container

Do not remove unit from overwrap until ready for use.

To open

Tear overwrap down side at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Preparation for Administration

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Table 2

Infusion Rate (mL/hr)

of Dobutamine Hydrochloride in 5% Dextrose Injection

500 mcg/mL

Patient's Weight (Kg)

Drug Delivery Rate (mcg/Kg/min)	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.3	0.6	1.2	1.8	2.4	3	3.6	4.2	4.8	5.4	6	6.6
1	0.6	1.2	2.4	3.6	4.8	6	7.2	8.4	9.6	10.8	12	13.2
2.5	1.5	3	6	9	12	15	18	21	24	27	30	33
5	3	6	12	18	24	30	36	42	48	54	60	66
7.5	4.5	9	18	27	36	45	54	63	72	81	90	99
10	6	12	24	36	48	60	72	84	96	108	120	132
12.5	7.5	15	30	45	60	75	90	105	120	135	150	165
15	9	18	36	54	72	90	108	126	144	162	180	198
17.5	10.5	21	42	63	84	105	126	147	168	189	210	231
20	12	24	48	72	96	120	144	168	192	216	240	264

1000 mcg/mL

Patient's Weight (Kg)

Drug Delivery Rate (mcg/Kg/min)	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.15	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3	3.3
1	0.3	0.6	1.2	1.8	2.4	3	3.6	4.2	4.8	5.4	6	6.6
2.5	0.75	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5
5	1.5	3	6	9	12	15	18	21	24	27	30	33
7.5	2.25	4.5	9	13.5	18	22.5	27	31.5	36	40.5	45	49.5
10	3	6	12	18	24	30	36	42	48	54	60	66
12.5	3.75	7.5	15	22.5	30	37.5	45	52.5	60	67.5	75	82.5
15	4.5	9	18	27	36	45	54	63	72	81	90	99
17.5	5.25	10.5	21	31.5	42	52.5	63	73.5	84	94.5	105	115.5
20	6	12	24	36	48	60	72	84	96	108	120	132

2000 mcg/mL

Patient's Weight (Kg)

Drug Delivery Rate (mcg/Kg/min)	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.08	0.15	0.3	0.45	0.6	0.75	0.9	1.05	1.2	1.35	1.5	1.65
1	0.15	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3	3.3
2.5	0.38	0.75	1.5	2	3	4	4.5	5	6	7	7.5	8
5	0.75	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	1.13	2.25	4.5	7	9	11	13.5	16	18	20	22.5	25
10	1.5	3	6	9	12	15	18	21	24	27	30	33
12.5	1.88	3.75	7.5	11	15	19	22.5	26	30	34	37.5	41
15	2.25	4.5	9	13.5	18	22.5	27	31.5	36	40.5	45	49.5
17.5	2.63	5.25	10.5	15.75	21	26.25	31.5	36.75	42	47.25	52.50	57.75
20	3	6	12	18	24	30	36	42	48	54	60	66

4000 mcg/mL

Patient's Weight (Kg)

Drug Delivery Rate (mcg/Kg/min)	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.04	0.08	0.15	0.23	0.3	0.38	0.45	0.53	0.6	0.68	0.75	0.83
1	0.08	0.15	0.3	0.45	0.6	0.75	0.1	1.05	1.2	1.35	1.5	1.65
2.5	0.19	0.38	0.75	1	1.5	2	2	2.5	3	3.5	4	4
5	0.38	0.75	1.5	2	3	4	4.5	5	6	7	7.5	8
7.5	0.56	1.13	2.25	3.5	4.5	5.5	7	8	9	10	11	12.5
10	0.75	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5
12.5	0.94	1.88	3.75	5.5	7.5	9.5	11	13	15	17	19	20.5
15	1.13	2.25	4.5	7	9	11	13.5	16	18	20	22.5	25
17.5	1.31	2.63	5.25	7.88	10.5	13.13	15.75	18.38	21	23.63	26.25	28.88
20	1.5	3	6	9	12	15	18	21	24	27	30	33

Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Printed in USA

7-19-4-854
Rev. December 1999

*BAR CODE POSITION ONLY

071904854

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20255/S6

ADMINISTRATIVE DOCUMENTS

JUN 14 2000

CSO Review of Final Printed Labeling

Application: NDA 20-255/S-006

Applicant: Baxter Healthcare Corporation

Date of Original Application: March 12, 1999

Date of Approvable Letter: June 16, 1999

Date of FPL Submission: April 27, 2000

Product Name: Dobutamine Hydrochloride and 5% Dextrose Injection, USP in Plastic Container, PL 2207

Background

NDA-20-255/S-006 provides for pediatric labeling changes made in response to the Final Rule published in the Code of the Federal Register on December 13, 1994 titled Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric use" Subsection in the Labeling. The Division issued an approvable letter (with marked-up draft labeling) on June 16, 1999 asking for pediatric-related changes in the **CLINICAL PHARMACOLOGY, INDICATIONS and USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and DOSAGE and ADMINISTRATION** sections of the labeling (see enclosure). This submission is in response to that letter.

Review

The sponsor submitted final printed labeling on April 27, 2000 that was identical to the changes requested by the Division in the June 16, 2000 approvable letter. An approval letter will be prepared for Dr. Lipicky's signature.

/S/

Edward Fromm
Consumer Safety Officer

dr/5-15-00

cc: NDA 20-255
HFD-110
HFD-110/EFromm
HFD-110/Blount

Enclosure

JUN 16 1999

LABELING REVIEW

NDA 20-255/S-006 Dobutamine Hydrochloride in 5% Dextrose Injection in Plastic Container

Sponsor: Baxter Healthcare Corporation
Round Lake, IL 60073

Date of Submission: March 12, 1999

BACKGROUND

The supplemental application was submitted in response to the December 13, 1999 Federal Register notice titled "Specific Requirements on content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling." The firm provided copies of 71 articles and five additional supporting documents to support their proposed revisions related to pediatric dosing.

REVIEW

Dr. Knudsen reviewed the application. A similar supplemental application, however, was submitted and approved by the dobutamine innovator, Eli Lilly. Dr. Lipicky decided that, in order to avoid confusion, there should not be two different sets of pediatric dosing guidelines. He therefore decided to incorporate the revisions from the Eli Lilly supplement into the Baxter labeling.

A labeling draft was prepared that incorporated the revisions made to the Dobutrex (dobutamine hydrochloride, Lilly) application (NDA 17-820/S-036) into the Baxter draft. An approvable letter will be prepared for Dr. Lipicky's signature.

/S/ 4/22/99

Gary Buehler
Project Manager

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

10.1

MAR 19 1999

NDA 20-255 Dobutamine Hydrochloride in 5% Dextrose

Proposal for pediatric labeling changes.

The sponsor submits reprints of 71 articles on the pediatric use of this substance.

Indications:
In neonates born prematurely and in children with congenital heart disease dopamine and dobutamine are used to combat shock and hypotension.

There seems to be a consensus that dopamine is superior in terms of raising MAP but that dobutamine has a more pronounced inotropic effect, and possibly a beneficial effect on renal function. Some authors therefore recommend a combination of the two in low doses, rather than increasing the dose of monotherapy. This use is such a specialized field that the practitioners are unlikely to rely on the package insert as the main source of information. There might be a note under 'Dosage and Administration' that at least one author warns against "wasting time" with starting doses of dopamine <10µg/kg/min in very sick children.

Recommendations:
I agree with insert A: and B:

Strike "essentially" in insert C:

Insert D: is misplaced; it should go in the "How Supplied" section. If there are "Other Dosage Forms" available they should be itemized; otherwise this sentence is not helpful.

3/19/1999 Knud Knudsen

/S/