

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number **74995**

Trade Name **Dobutamine Injection USP 12.5mg/ml 100ml**
Pharmacy Bulk Package

Generic Name **Dobutamine Injection USP 12.5mg/ml 100ml**
Pharmacy Bulk Package

Sponsor **Marsam Pharmaceuticals, Inc.**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 744995

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **74995**

APPROVAL LETTER

ANDA 74-995

MAR 31 1998

Marsam Pharmaceuticals, Inc.
Attention: Steven W. Brown
Building 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, NJ 08034

Dear Sir:

This is in reference to your abbreviated new drug application dated October 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dobutamine Injection USP, 12.5 mg/mL; 100 mL Pharmacy Bulk Package.

Reference is also made to your amendments dated November 1, 1996; August 6, 1997; and February 5, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dobutamine Injection USP, 12.5 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, (Dobutrex Injection, 12.5 mg/mL, of Eli Lilly and Co.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Sporn
3-31-98

cc: ANDA 74-995
Division File
FIELD COPY
HFD-610/JPhillips
HFD-92
HFD-210/B.Poole
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→ HFD-305

Endorsements:
HFD-623/D.Gill/3/6/
HFD-623/V.Sayer
HFD-617/J.Wilson
HFD-640/A.High
HFD-613/C.Park
HFD-613/J.Grace

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F/T by: gp/3/13/98

3/30/98

APPROVAL

3/23/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74995

FINAL PRINTED LABELING

Maize

BULK

NDC 0209-2682-50

DOBUTAMINE 1.25 grams
Injection, USP

PHARMACY BULK PACKAGE — NOT FOR DIRECT INFUSION

Equivalent to 1.25 grams DOBUTAMINE per 100 mL (12.5 mg/mL)

MUST BE DILUTED PRIOR TO USE FOR IV USE ONLY

Do not dispense as a unit.

Marsam
PHARMACEUTICALS, INC.
Cherry Hill, NJ 08034

75 mL
Approximate Volume
50 mL

Each mL contains: Dobutamine hydrochloride, equivalent to 12.5 mg dobutamine, and sodium metabisulfite 0.24 mg (added during manufacture). In Water for Injection, pH 2.5-5.5; hydrochloric acid and/or sodium hydroxide added, if needed, for pH adjustment.

Usual Dosage: This pharmacy bulk package is intended for preparing IV infusions only. See insert for further information on dilution, dosage and administration.

Use diluted solution within 24 hours after dilution.

Contains the following Preservatives: Benzalkonium Chloride. Once the container closure has been punctured, withdrawal of the contents should be completed without delay. If prompt fluid transfer can not be accomplished, discard the contents no later than 4 hours after initial closure puncture.

Dispense aliquots from the vial via a suitable dispensing technique. Store in infusion fluids under a laminar flow hood using aseptic technique.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Date Entered: _____
Time of Entry: _____

DOBUTAMINE 1.25 grams

3 0209 - 2682 - 50 9

BULK

25 mL
Approximate Volume
50 mL

3 0209 - 2682 - 50 9

BULK

NDC 0209-2682-50

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BULK

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Approximate Volume
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3 0209 - 2682 - 50 9

31

APPROVED

BULK

NDC 0209-2682-52
10 vials • 100 mL

1.25
grams

DOBUTAMINE
Injection, USP

PHARMACY BULK PACKAGE — NOT FOR DIRECT INFUSION

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(12.5 mg/mL)

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FOR IV USE ONLY.

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Marsam
PHARMACEUTICALS INC.
Cherry Hill, NJ 08034

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DOBUTAMINE
Injection, USP

NOT FOR DIRECT INFUSION

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FOR IV USE ONLY.

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ALS INC.
08034

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BULK

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Marsam

PHARMACEUTICALS INC.
Cherry Hill, NJ 08034

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DIRECT INFUSION

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Equivalent to 1.25 gr

PHARMACY BULK PACK/

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NDC 0209-2682-52
10 vials • 100 mL

BULK

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IV admixtures only. See insert for further information on

container contents should be completed without delay.
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infusion fluids under a laminar flow hood using aseptic

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52 3

BULK

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Marsam
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Cherry Hill, NJ 08034

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Use diluted solution within 24 hours after dilution.

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PHARMACEUTICALS INC.
Cherry Hill, NJ 08034





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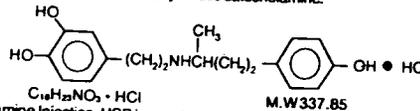


DOBUTAMINE INJECTION, USP

Pharmacy Bulk Package—Not for Direct Infusion

DESCRIPTION

Dobutamine Injection, USP is (+)-4-[2-[[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride. It is a synthetic catecholamine.



Dobutamine Injection, USP is supplied as a sterile solution for intravenous use only. Each mL contains: 12.5 mg (41.5 μ mol) dobutamine as dobutamine hydrochloride, 0.24 mg sodium metabisulfite (added during manufacture), in Water for Injection, q.s. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust the pH (pH 2.5 to 5.5).

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents of this pharmacy bulk package are intended for use by a pharmacy admixture service for addition to suitable parenteral fluids in the preparation of admixtures for intravenous infusion (see **DOSAGE AND ADMINISTRATION**).

CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the beta 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 Injection, USP 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 in humans is 2 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.

INDICATIONS AND USAGE

Dobutamine Injection, USP 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.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutamine Injection, USP.

CONTRAINDICATIONS

Dobutamine Injection, USP is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutamine Injection, USP.

WARNINGS

- Increase in Heart Rate or Blood Pressure**
Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of 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 promptly 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.
- Ectopic Activity**
Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.
- Hypersensitivity**
Reactions suggestive of hypersensitivity associated with administration of Dobutamine Injection, USP, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.
- Dobutamine Injection, USP contains sodium metabisulfite, 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.**

PRECAUTIONS

General

- During the administration of Dobutamine Injection, USP 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 Injection, USP.
- Hypotension should be corrected with suitable volume expansion.

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4. Dobutamine Injection, USP contains sodium metabisulfite, 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.

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General

1. During the administration of Dobutamine Injection, USP 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 Injection, USP.
2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutamine Injection, USP is instituted.
3. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

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 increases in contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Laboratory Tests

Dobutamine, like other beta₁-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.

Drug Interactions

Animal studies indicate that dobutamine may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase. 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. 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, nitroglycerin, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the carcinogenic or mutagenic potential of dobutamine, or its potential to affect fertility, have not been conducted.

Pregnancy: Teratogenic Effects: Pregnancy Category B

Reproduction studies performed in rats at doses up to the normal human dose (10 mcg/kg/min for 21 h, total daily dose of 14.4 mg/kg) and in rabbits at doses up to twice the normal human dose have revealed no evidence of harm to the fetus due to dobutamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of Dobutamine Injection, USP on labor and delivery is unknown.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Dobutamine Injection, USP is administered to a nursing woman. If a mother requires dobutamine treatment, breast-feeding should be discontinued for the duration of the treatment.

Pediatric Use

The safety and effectiveness of Dobutamine Injection, USP for use in pediatric patients have not been studied.

ADVERSE REACTIONS

Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity: A 10 to 20 mm 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 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. Isolated cases of cutaneous necrosis (destruction of skin tissue) have been reported.

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

Isolated cases of thrombocytopenia have been reported. Administration of Dobutamine Injection, USP, like other catecholamines, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels (see PRECAUTIONS).

Longer-Term Safety: Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

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 beta-receptor stimulation. The duration of action of dobutamine is generally short ($T_{1/2} = 2$ 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.

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 overdose, 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.

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

This insert is for a Pharmacy Bulk Package and is intended for preparing IV admixtures only. Dosage recommendations for intravenous injection are for informational purposes only.

Note: Do not add Dobutamine Injection, USP to 5% Sodium Bicarbonate Injection or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended that Dobutamine Injection, USP not be mixed with other drugs in the same solution. Dobutamine Injection, USP should not be used in conjunction with other agents or diluents containing both sulfites and ethanol.

Directions for Proper Use of Pharmacy Bulk Package—Not for Direct Infusion

1. Use of this product is restricted to a suitable work area, such as a laminar flow hood.
2. Using aseptic technique, the closure should be penetrated only one time using a suitable sterile dispensing set which allows measured dispensing of the contents. Use of a syringe and needle is not recommended as it may cause leakage.
3. Once the container closure has been punctured, withdrawal of the contents should be completed without delay. THE ENTIRE CONTENTS OF THE VIAL SHOULD BE DISPENSED WITHIN 4 HOURS OF INITIAL ENTRY. Use the bail band supplied with the vial to hang this container and use a dispensing set which allows measured dispensing of the contents.

THIS PACKAGE IS NOT TO BE DISPENSED AS A UNIT.

Preparation and Stability

Within 24 hours prior to administration, withdraw the portion of the Pharmacy Bulk Package vial containing the desired dose and add it to an IV container. Dobutamine Injection, USP must be diluted to at least 5 mcg/mL (see Recommended Dosage). Use one of the following: 5% Dextrose Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 10% Dextrose Injection, Isolyte® M with 5% Dextrose Injection, Lactated Ringer's Injection, 5% Dextrose in Lactated Ringer's Injection, Normoso®-M in D5-W, 20% Osmitrol® in Water for Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Recommended Dosage

The rate of infusion needed to increase cardiac output usually ranged from 2.5 to 15 mcg/kg/min (see Table 1). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Table 1
Dobutamine Injection, USP
Infusion Rate (mL/kg/min) for Concentrations of
250, 500, and 1,000 mcg/mL

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate		
	250 mcg/mL* (mL/kg/min)	500 mcg/mL** (mL/kg/min)	1,000 mcg/mL*** (mL/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

* 250 mcg/mL of diluent

** 500 mcg/mL or 250 mg/500 mL of diluent

*** 1,000 mcg/mL or 250 mg/250 mL of diluent

Rates of infusion in mL/h for dobutamine concentrations of 500 mcg/mL, 1,000 mcg/mL, and 2,000 mcg/mL are given in Table 2.

Table 2
Dobutamine Injection, USP Infusion Rate (mL/h)
for 500 mcg/mL concentration

Drug Delivery Rate	Patient Body Weight (kg)
--------------------	--------------------------

10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

4

* 250 mcg/mL of diluent
 ** 500 mcg/mL or 250 mg/500 mL of diluent
 *** 1,000 mcg/mL or 250 mg/250 mL of diluent
 Rates of infusion in mL/h for dobutamine concentrations of 500 mcg/mL, 1,000 mcg/mL, and 2,000 mcg/mL are given in Table 2.

Table 2
 Dobutamine Injection, USP Infusion Rate (mL/h)
 for 500 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)								
	30	40	50	60	70	80	90	100	110
2.5	9	12	15	18	21	24	27	30	33
5	18	24	30	36	42	48	54	60	66
7.5	27	36	45	54	63	72	81	90	99
10	36	48	60	72	84	96	108	120	132
12.5	45	60	75	90	105	120	135	150	165
15	54	72	90	108	126	144	162	180	198

Dobutamine Injection, USP Infusion Rate (mL/h)
 for 1,000 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)								
	30	40	50	60	70	80	90	100	110
2.5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
5	9	12	15	18	21	24	27	30	33
7.5	13.5	18	22.5	27	31.5	36	40.5	45	49.5
10	18	24	30	36	42	48	54	60	66
12.5	22.5	30	37.5	45	52.5	60	67.5	75	82.5
15	27	36	45	54	63	72	81	90	99

Dobutamine Injection, USP Infusion Rate (mL/h)
 for 2,000 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)								
	30	40	50	60	70	80	90	100	110
2.5	2	3	4	4.5	5	6	7	7.5	8
5	4.5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	7	9	11	13.5	16	18	20	22.5	25
10	9	12	15	18	21	24	27	30	33
12.5	11	15	19	22.5	26	30	34	37.5	41
15	13.5	18	22.5	27	31.5	36	40.5	45	49.5

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.

Concentrations up to 5,000 mcg/mL have been administered to humans (250 mg/50 mL). The final volume administered should be determined by the fluid requirements of the patient.

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

HOW SUPPLIED

Dobutamine Injection, USP containing 1.25 grams dobutamine (as the hydrochloride) is available as follows:

NDC 0209-2682-62—100 mL vial, Pharmacy Bulk Package, packaged in 10s.

Storage

Store at controlled room temperature, 15°–30°C (59°–86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Marsam Pharmaceuticals Inc.

Cherry Hill, NJ 08034

Issued 7-97

C2682

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74995

SEE ANDA 74279 FOR CHEMISTRY REVIEW

CHEMISTRY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74995

BIOEQUIVALENCE REVIEW(S)

ANDA 74-995

Marsam Pharmaceuticals, Inc.
Attention: Thomas L Pituk
Building 31,
24 Olney Avenue
P.O. Box 1022
Cherry Hill NJ 08034

MAR 13 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Dobutamine Hydrochloride Injection USP, 12.5 mg (base)/mL, 100 mL Vial.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

fn Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR 4 1997

Dobutamine Hydrochloride Injection
12.5 mg base/mL 100 mL fill
ANDA #74-995
Reviewer: Moo Park
File name: 74995W.o96

Marsam Pharmaceuticals
Cherry Hill, NJ
Submission Date:
October 31, 1996

Review of a Waiver Request

I. Objective

Review of Marsam Pharmaceuticals' request for a waiver of *in vivo* bioequivalence study requirements for its test product Dobutamine Hydrochloride Injection, USP, 12.5 mg base/mL in 100 mL fill vials. Innovator product is Dobutrex^R manufactured by Eli Lilly.

Marsam's Dobutamine Hydrochloride Injection, USP, 12.5 mg base/mL in 20 mL fill vials (ANDA #74-279) was granted a waiver.

II. Comments

1. Dobutamine Hydrochloride Injection, USP, is an aqueous injectable solution for IV infusion. The test and reference products contain the same amount (12.5 mg base/mL) of the active ingredient. However, the test product contains sodium metabisulfite instead of sodium bisulfite which is used in the reference product. The monograph of sodium bisulfite of NF XV reads "Note-Where Sodium Bisulfite is called for, use Sodium Metabisulfite." The monograph of sodium bisulfite was deleted from NF XVI and NF XVII. The pH range of the test product is
Table 1 shows the formulations of the test and reference products:

Table 1. Comparison of Formulations
 Dobutamine Hydrochloride Injection, USP
 (Unit: mg/mL)

<u>Ingredients</u>	<u>Test Product</u>	<u>Ref Product</u>
Dobutamine HCl (as base)	12.5	12.5
Sodium Metabisulfite	0.24	-
Sodium Bisulfite	-	0.24
0.1 N NaOH or HCl for pH adjustment	qs	qs
Water for Injection qs ad	1.0 mL	1.0 mL

2. The waiver is granted.

III. Deficiency

None.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Marsam Pharmaceuticals demonstrates that Dobutamine Hydrochloride Injection, USP, 12.5 mg/mL packaged in 100 mL fill vials falls under 21 CFR Section 320.22 (b) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product to be bioequivalent to Dobutrex^R Injection, 12.5 mg/mL packaged in 100 mL fill vials manufactured by Eli Lilly.

The firm should be informed of the recommendation.

Moo Park, Ph.D.
 Chemist, Review Branch III
 Division of Bioequivalence

RD INITIALED RMHATRE
 FT INITIALED RMHATRF
 Ramakant M. Mhatre, Ph.D.
 Team Leader, Review Branch III
 Division of Bioequivalence

— 2/27/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74995

MICROBIOLOGY REVIEW(S)

1. /

DIVISION OF CHEMISTRY I
OFFICE OF GENERIC DRUGS

Microbiologist's Review #1

December 16, 1996

A. 1. ANDA: 74-995

APPLICANT: Marsam Pharmaceuticals, Inc.
Attention: Thomas L Pituk
Building 31, Olney Avenue
P.O. Box 1022
Cherry Hill, New Jersey 08034

2. PRODUCT NAMES: **Dobutamine Injection USP**
[Pharmacy Bulk Package]

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Sterile solution for injection **12.5 mg/mL** [1.25 g/100 mL];
100 mL fill contained in 100 mL vials

4. METHOD(S) OF STERILIZATION:

5. PRINCIPLE INDICATIONS: Parenteral therapy for inotropic support in the short-term treatment of adults with cardiac decompensation.

6. PHARMACOLOGICAL CATEGORY: Inotropic agent

B. 1. DATE OF INITIAL SUBMISSION:

October 31, 1996 (Received by OGD on 11/1/96)
- Subject of this review

2. DATE OF AMENDMENT: N/A; no amendments containing sterility assurance information were received by the time this document was reviewed

3. RELATED DOCUMENTS:

ANDA 74-279 held by the applicant for Dobutamine Hydrochloride Injection in 20 mL single dose vials [Recommended for approval by KHMuhvich on October 30, 1994 with respect to sterility assurance]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74995

CORRESPONDENCE

Marsam
PHARMACEUTICALS INC.

ORIG AMENDMENT

N/AM

February 5, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA 74-995**
Dobutamine Injection USP, 12.5 mg/mL, 100 mL vial (Pharmacy Bulk Package)
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to our abbreviated new drug application dated October 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations 21 CFR§314.94 for Dobutamine Injection USP, 12.5 mg/mL, 100 mL vial (PBP).

Reference is also made to your not approvable letter dated August 19, 1997, stating that the application was deficient and, therefore, not approvable under 21 CFR§314.125(b)(13). Your letter stated that, based on an April 22, 1997 to June 6, 1997 inspection, CDER had determined that Marsam was not in compliance with current good manufacturing practice (CGMP) regulations. Your letter stated that, until such time that we can demonstrate that the problems have been corrected, the application cannot be approved. In addition, you directed us to submit a MINOR AMENDMENT in response to the not approvable letter which includes a statement from a responsible corporate official certifying that our facilities have been found to be in compliance with CGMP and cleared for approval of this drug product by representatives of the local FDA District Office.

In accordance with your request and pursuant to 21 CFR§314.96, we are submitting this MINOR AMENDMENT to provide a statement certifying that our facilities have been reinspected and found to be in compliance with CGMP regulations and cleared for approval of this (and all) drug products by representatives of New Jersey District Office. We are also enclosing a copy of the "Profile System" printout that was supplied to us on February 3, 1997, by Mr. Richard T. Trainor, Compliance Officer, of the NJD.

RECEIVED
FEB 06 1998

[Handwritten signature]

GENERIC DRUGS

ANDA 74-995

Page 2

Dobutamine Injection USP, 12.5 mg/mL, 100 mL vial (Pharmacy Bulk Package)
MINOR AMENDMENT

We certify that a true copy of this amendment is being sent to our local FDA District Office.

Please advise us if you require any additional information.

Sincerely,
Marsam Pharmaceuticals Inc.



Steven W. Brown, R.Ph.
Director, Regulatory Affairs

SWB

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

Marsam

PHARMACEUTICALS INC.

October 31, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

RECEIVED

NOV 01 1996

GENERIC DRUGS

Re: **NEW ANDA**
Dobutamine Injection, USP - 1.25 grams/100 mL (12.5 mg/mL)
100 mL vial, Pharmacy Bulk Package

Dear Sir/Madam:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting the attached Abbreviated New Drug Application (ANDA) for the above referenced product. The listed drug upon which this application is based is Dobutrex[®] Solution (Dobutamine Hydrochloride Injection) by Eli Lilly and Co. Please note that this ANDA is also based on a suitability petition submitted and approved by FDA for the 100 mL Pharmacy Bulk Package size of Dobutamine Injection, USP (Section II). This petition requested permission to file an ANDA for the 12.5 mg/mL, 100 mL product based on Eli Lilly's 12.5 mg/mL, 20 mL Dobutrex[®] Solution (Dobutamine Hydrochloride Injection). In addition, in accordance with the new nomenclature listed in USP 23 Supplement 5, effective November 15, 1996, the application and labeling have been submitted as Dobutamine Injection, USP. Draft labeling is included (Section V) which is based on current approved labeling for Dobutrex[®] Solution (Dobutamine Hydrochloride Injection).

Please note that ANDA 74-279 for Dobutamine Hydrochloride Injection, 12.5 mg/mL, was submitted by Marsam November 24, 1992 (prior to the nomenclature revision) for the 20 mL single dose vial. Therefore, since both the 20 mL and 100 mL drug products contain the same strength but in different fill sizes, the 100 mL application is similar to the 20 mL application except where outlined. Please note that the exhibit batch contained in this application contains active drug substance, Dobutamine Hydrochloride, USP, manufactured and supplied by
to This revision contained changes in the manufacturing of
Dobutamine Hydrochloride, USP. Therefore, relevant issues concerning exhibit
batches using the active drug substance manufactured by
revision have been addressed in the 20 mL application and are not applicable in the

100 mL application. Please note that the draft package insert included in this application contains both the proposed 20 mL and 100 mL presentations of Dobutamine Injection, USP.

This submission consists of two (2) volumes. As required, archival and review copies are provided, and a true copy of the ANDA is being sent concurrently to our home district FDA office. (Please refer to Section XXI for the District Copy Certification and Debarment Certification.) In addition, to facilitate the microbiological review, pertinent information has been placed in Section XI.2 of the ANDA. A request for waiver of bioequivalence testing is located in Section VI.1.

Included in Section XVII are stability data for the product in the 100 mL vial. Based on the data, we are proposing a 24 month expiration date for this product.

During the course of your review of this application, if you have any questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact

Jill Kompa
Phone: (609) 424-5600, Ext. 330
Fax: (609) 751-8784

Alternate Contact

Anne Toland
Phone: (609) 424-5600, Ext. 249
Fax: (609) 751-8784

Sincerely,



Thomas L. Pituk
Director, Regulatory Affairs

Enclosures

cc: FDA Newark District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902