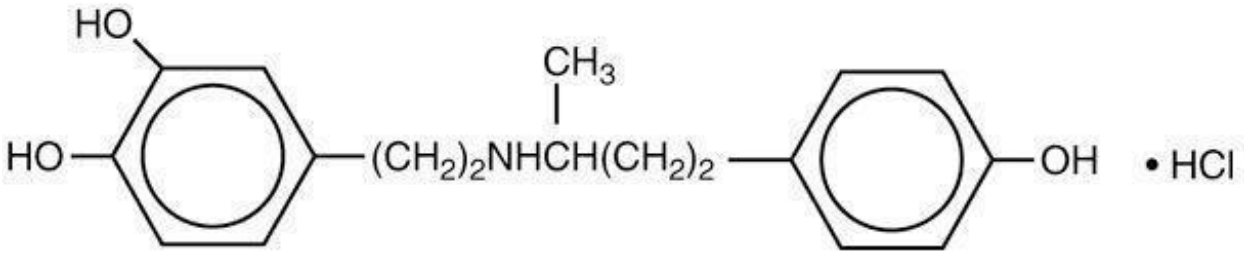
DOBUTAMINE- dobutamine hydrochloride injection injection, solution
General Injectables and Vaccines, Inc.

DOBUTAMINE

DESCRIPTION

Dobutamine Injection, USP is 1,2-benzenediol, 4-[2-[[3-(4-hydro-xphenyl)-1-methylpropyl]amino]ethyl]-hydrochloride, (±). It is a synthetic catecholamine.



Molecular Formula: $C_{18}H_{23}NO_3 \cdot HCl$ Molecular Weight: 337.85

The clinical formulation is supplied in a sterile form for intravenous use only. Each mL contains: Dobutamine hydrochloride, equivalent to 12.5 mg (41.5 umol) dobutamine; 0.24 mg sodium metabisulfite (added during manufacture), and water for injection, pH adjusted between 2.5 to 5.5 with hydrochloric acid and/or sodium hydroxide. Dobutamine is oxygen sensitive.

CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not ccause 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 bolume 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 clincical 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 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 3-0-methyl dobutamine. The 3-0 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 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 use prior to institution of therapy with dobutamine hydrochloride.

CONTRAINDICATIONS

Dobutamine hydrochloride is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to dobutamine injection.

WARNINGS

1. Increase in Heart Rate or Blood Pressure

Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic 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.

2. Ectopic Activity

Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. Hypersensitivity

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

4. Dobutamine injection 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 sulfit sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

1. During the administration of dobutamine 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 hydrochloride.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with dobutamine 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 injection 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 siaze of an infarction by intensiftying ischemia, but it is not known whether dobutamine does so.

Laboratory Tests- Dobutamine, like other β2-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 studiesindicate that dobutamine may be ineffective if the patient has recently received a β-blocking drug. In such a case, the peripheral vascular resistance may increase.

Preliminary studies indicate that the concimtant use of dobutamine and nitroprusside results in a higher cardiac output and, ususally, a lower pulmonary wedge pressure than when either drug is used alone.

There was no evidence of drug interactions in clincial sutdies 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 hydrochloride, 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 hjman dose (10 mcg/kg/min for 24 h, total daily dose of 14.4 mg/kg) and in rabbits at doses up to 2 times 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 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 hydrochloride 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 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 pateints have had increased premature ventricular beats during infusions. These effects are dose related.

Hypotension- Preciipitous 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, 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 hydrochloride is usually due to excessive cardiac β receptor stimulation. The duration of action of dobutamine hydrochloride is generally short (T1/2 = 2 minutes) because it is repidly metabolized by catechol-0-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 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 hydrochloride overdose are discontinuing administration, establishing and 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 infested, 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 of labage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten eliminiation of some drugs that have been absorbed. Safeguard the patient's airway when employing gastirc emptying or charcoal.

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

DOSAGE AND ADMINSTRATION

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

Preparation and Stability- At the time of administration, dobutamine injection must be further diluted in an IV container: Dilute 20 mL of dobutamine in at least 50 mL of diluent and dilute 40 mL of dobutamine in at least 100 mL of diluent. Use one of the following intravenous solutions as a diluent: Dextrose Injection 5%, Dextrose 5% and Sodium Chloride 0.45% Injection, Dextrose 5% and Sodium Chloride 0.9% Injection, Dextrose Injection 10%, Isolyte® M with 5% Dextrose Injection, Lactated Ringer's

Injection, 5% Dextrose in Lactated Ringer's Injection, Normosol®-M in D5-W, 20% Osmitrol® in Water for Injection, Sodium Chloride Injection 0.9%, 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). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Dobutamine Injection
Rates of Infusion for Concentrations of 250, 500, and 1,000 mcg/mL

Drug Delivery Rate	Infusion Delivery Rate		
	250 mcg/mL*	500 mcg/mL†	1,000 mcg/mL‡
(mcg/kg/min)	(mL/kg/min)	(mL/kg/min)	(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 Injection concentrations of 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL are given in Table 2.

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

Drug Delivery Rate	Patient Body Weight (kg)								
(mcg/kg/min)	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 Infusion Rate (mL/h) for 1,000 mcg/mL concentration

Drug Delivery Rate	Patient Body Weight (kg)								
(mcg/kg/min)	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 Infusion Rate(mL/h) for 2,000 mcg/mL concentration

Drug Delivery Rate	Patient Body Weight (kg)								
(mcg/kg/min)	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 oof 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 of 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, 12.5 mg/mL is available as:

20 mL Single-Dose Vials containing 250 mg dobutamine (as the hydrochloride), boxes of 10 (List 2025).

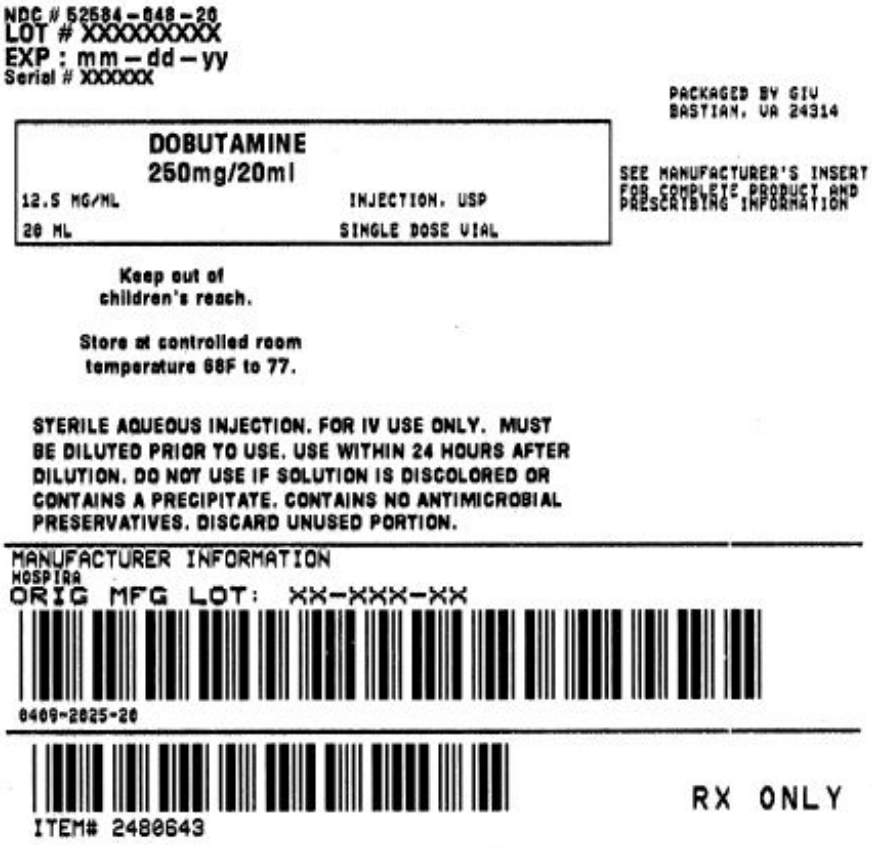
40 mL Single-Dose Vials containing 500 mg dobutamine (as the hydrochloride), boxes of 10 (List 2025).

Store at 20 to 25C (68 to 77F). [See USP Controlled Room Temperature.]

Revised: January, 2005.

HOSPIRA, INC., Lake Forest, IL 60045 USA

SAMPLE PACKAGE LABEL



DOBUTAMINE

dobutamine hydrochloride injection injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:52584-048(NDC:0409-2025)
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DOBUTAMINE HYDROCHLORIDE (UNII: 0WR771DJXV) (DOBUTAMINE - UNII:3S12J47372)	DOBUTAMINE	12.5 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	0.24 mg in 1 mL
WATER (UNII: 059QF0KO0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52584-048-20	1 in 1 BAG	11/10/2014	
1		20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074292	11/10/2014	

Labeler - General Injectables and Vaccines, Inc. (108250663)

Revised: 9/2017 General Injectables and Vaccines, Inc.