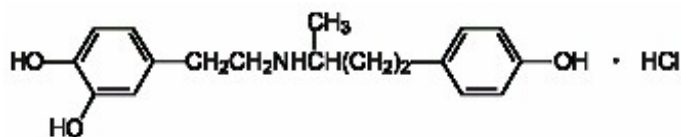


DOBUTAMINE- dobutamine injection, solution
Hikma Pharmaceuticals USA Inc.

DOBUTamine Injection USP
Rx ONLY

DESCRIPTION

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



Molecular Formula: C₁₈H₂₃NO₃•HCl

Molecular Weight: 337.84

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 μ mol) dobutamine; sodium metabisulfite 0.26 mg, and water for injection, q.s. Hydrochloric acid and/or sodium hydroxide may have been added during manufacture to adjust the pH (2.5 to 5.5).

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 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 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.

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 **PRECAUTIONS**, *Pediatric Use*).

INDICATIONS AND USAGE

Dobutamine 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. 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 risk of hospitalization and death. Patients with NYHA Class IV symptoms appeared to be at particular risk.

CONTRAINDICATIONS

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

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 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 promptly reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine. 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 including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

Dobutamine 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

1. **During the administration of dobutamine, 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.**
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 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.

Laboratory Tests

Dobutamine, like other β_2 -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 β -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, glyceryl trinitrate, 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 24 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 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 is administered to a nursing woman. If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

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.

Geriatric Use

Of the 1893 patients in clinical studies who were treated with dobutamine, 930 (49.1%) were 65 and older. No overall differences in safety or effectiveness were observed between these and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

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, like other catecholamines, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels (see **PRECAUTIONS**).

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 β -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

Note- Do not add dobutamine to 5% Sodium Bicarbonate Injection or to any other strongly alkaline solution. Because of potential physical incompatibilities, it is recommended that dobutamine not be mixed with other drugs in the same solution. Dobutamine 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 must be further diluted in an IV container to at least a 50 mL solution using one of the following intravenous solutions as a diluent: 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, Normosol[®]-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

Infusion of dobutamine should be started at a low rate (0.5 to 1 mcg/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 to 20 mcg/kg/min but sometimes slightly outside of this range. On rare occasions, infusion rates up to 40 mcg/kg/min have been required

to obtain the desired effect. Rates of infusion (mL/h) for dobutamine concentrations of 500 mcg/mL, 1000 mcg/mL, and 2000 mcg/mL necessary to attain various delivery rates of dobutamine (mcg/kg/min) for patients of different weights are given in Table 1.

Table 1 Dobutamine Injection USP Infusion Rate (mL/h) for 500 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)											
	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

Dobutamine Injection USP Infusion Rate (mL/h) for 1000 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)											
	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.1	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	0.7	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	2.2	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	3.7	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	5.2	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

Dobutamine Injection USP Infusion Rate (mL/h) for 2000 mcg/mL concentration

Drug Delivery Rate (mcg/kg/min)	Patient Body Weight (kg)											
	5	10	20	30	40	50	60	70	80	90	100	110
0.5	0.07	0.1	0.3	0.4	0.6	0.7	0.9	1	1.2	1.3	1.5	1.6
1	0.1	0.3	0.6	0.9	1.2	1.5	1.8	2.1	2.4	2.7	3	3.3
2.5	0.4	0.7	1.5	2	3	4	4.5	5	6	7	7.5	8
5	0.7	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5
7.5	1.1	2.2	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	1.9	3.7	7	11	15	19	22.5	26	30	34	37.5	41
15	2.2	4.5	9	13.5	18	22.5	27	31.5	36	40.5	45	49.5
17.5	2.6	5.2	10.5	15.7	21	26.2	31.5	36.7	42	47.2	52.5	57.7
20	3	6	12	18	24	30	36	42	48	54	60	66

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, 20 mL single dose vial contains dobutamine hydrochloride, equivalent to 250 mg dobutamine per 20 mL; ten vials per carton. **NDC 0143-9141-10.**

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

Manufactured by:

HIKMA FARMACÊUTICA (PORTUGAL), S.A.

Estrada do Rio da Mó, 8, 8A e 8B – Fervença – 2705-906 Terrugem SNT, PORTUGAL

Distributed by:

Hikma Pharmaceuticals USA Inc.

Berkeley Heights, NJ 07922

September

2022

WES/1

PIN612-

PRINCIPAL DISPLAY PANEL

NDC 0143-9141-01 Rx only

DOBUTamine Injection, USP

250 mg per 20 mL (12.5 mg/mL)

For Intravenous Use ONLY

Must be diluted prior to use

Use within 24 hours after dilution

20 mL Single-Dose Vial

NDC 0143-9141-01 Rx only

**DOBUTamine
Injection USP**

**250 mg per 20 mL
(12.5 mg/mL)**

For Intravenous Use ONLY
Must be diluted prior to use
Use within 24 hours after dilution

20 mL Single-Dose Vial

Each mL contains: Dobutamine hydrochloride, equivalent to 12.5 mg dobutamine; sodium metabisulfite 0.26 mg; Water for Injection, q.s., 1 mL. Hydrochloric Acid and/or Sodium Hydroxide may have been added to adjust pH between 2.5 to 5.5.

USUAL DOSAGE: For further dilution, dosage and administration, see package insert.

DISCARD UNUSED PORTION

CONTAINS NO ANTIMICROBIAL PRESERVATIVES

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

Mid. by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Dist. by: Hikma, Berkeley Heights, NJ 07922

(01)00301430141013

PLB247-WES/1

Lot:
Exp:

NDC 0143-9141-10 Rx only

**DOBUTamine
Injection, USP**

250 mg per 20 mL (12.5 mg/mL)

For Intravenous Use ONLY

Must be diluted prior to use

Use within 24 hours after dilution

10 x 20 mL Single-Dose Vials

To open - Cut seal along dotted line.

PLB249-WES/1
NDC 0143-9141-10 Rx only

**DOBUTamine
Injection, USP**

**250 mg per 20 mL
(12.5 mg/mL)**

For Intravenous Use ONLY
Must be diluted prior to use
Use within 24 hours after dilution

10 x 20 mL Single-Dose Vials

Each mL contains: Dobutamine hydrochloride, equivalent to 12.5 mg dobutamine; sodium metabisulfite 0.26 mg; Water for Injection, q.s., 1 mL. Hydrochloric Acid and/or Sodium Hydroxide may have been added to adjust pH between 2.5 to 5.5.


USUAL DOSAGE: For further dilution, dosage and administration, see package insert.

DISCARD UNUSED PORTION
CONTAINS NO ANTIMICROBIAL PRESERVATIVES
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].


Mfd. by: HIKMA FARMACÊUTICA (PORTUGAL), S.A.
Estrada do Rio da Mó, 8, 8A e 8B – Fervença –
2705-906 Terrugem SNT, PORTUGAL

Dist. by: Hikma, Berkeley Heights, NJ 07922

hikma.



SERIALIZATION IMAGE



GTIN 00301234567896
SN 1234567890123
EXP MMMYYY
LOT ABCDE12345

DOBUTAMINE

dobutamine injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0143-9141
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)	.26 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9141-10	10 in 1 CARTON	05/03/2023	
1		20 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074277	05/03/2023	

Labeler - Hikma Pharmaceuticals USA Inc. (001230762)**Registrant** - Hikma Pharmaceuticals USA Inc. (001230762)

Revised: 5/2023

Hikma Pharmaceuticals USA Inc.