PRODUCT MONOGRAPH

PrDOBUTAMINE INJECTION USP

Dobutamine (as Dobutamine Hydrochloride)

12.5 mg/mL
Sterile Solution for Injection

Sympathomimetic

SteriMax Inc.
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THERAPEUTIC CLASSIFICATION

Sympathomimetic

ACTION AND CLINICAL PHARMACOLOGY

Dobutamine is a direct-acting inotropic agent whose primary activity results from stimulation of the β -receptors of the heart while producing less marked chronotropic, hypertensive, arrhythmogenic or vasodilatory effects. Dobutamine, unlike dopamine, does not cause the release of endogenous norepinephrine. No specific effect on the renal vasculature has been observed. Dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol as demonstrated in both animal and human studies.

The onset of action is within 1 to 2 minutes, although the peak effect of a particular infusion may not be reached for 10 minutes. The plasma half-life in humans is 2 minutes.

INDICATIONS AND CLINICAL USE

Dobutamine Injection USP is indicated in the treatment of adults with cardiac decompensation due to depressed contractility resulting from organic heart disease or following cardiac surgical procedures in which parenteral therapy is necessary for inotropic support.

Most clinical experience with dobutamine is short-term -- up to 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 the output of others returned toward baseline values.

CONTRAINDICATIONS

Dobutamine Injection USP is contraindicated in patients with pheochromocytoma, idiopathic hypertrophic subaortic stenosis, and in those patients with hypersensitivity to dobutamine.

WARNINGS

Dobutamine Injection USP may cause a marked increase in heart rate or blood pressure, especially systolic pressure. About 10% of patients in clinical studies have had rate increases of 30 beats per minute or more, while about 7.5% have had a 50 mm Hg or greater increase in systolic pressure. Patients with pre-existing hypertension appear to have an increased risk of developing an exaggerated pressor response. A reduction of the dosage usually reverses these effects promptly.

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

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, in certain susceptible people.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutamine Injection USP. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response.

Dobutamine Injection USP should not be used in the presence of uncorrected tachycardia or

ventricular fibrillation.

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

Minimal vasoconstriction has occasionally been observed, most notably in patients recently treated with a β-blocking drug. Because the inotropic effect of Dobutamine Injection USP stems from stimulation of cardiac β_1 receptors, this effect is, of course, prevented by β-blocking drugs.

PRECAUTIONS

General: During the administration of Dobutamine Injection USP, as with any adrenergic agent, EKG, heart rate and blood pressure should be continuously monitored. In addition, the monitoring of pulmonary wedge pressure and cardiac output should be performed whenever possible to aid in the safe and effective infusion of Dobutamine Injection USP.

Caution should be exercised in order to prevent infiltration at the injection site.

Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutamine Injection USP.

Dobutamine Injection USP should be used with caution in patients with hyperthyroidism.

Caution should be exercised in patients receiving anesthetic agents, cyclopropane or halogenated hydrocarbons.

Caution should also be used in patients taking concomitantly other sympathomimetic amines.

Dobutamine Injection USP, like other β_2-agonists, can produce a mild reduction in serum

potassium concentration although rarely to hypokalemic levels. Accordingly, monitoring of serum potassium should be considered.

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

Usage in Pregnancy: Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to dobutamine. To date, the drug has not been administered to pregnant women and should be used in such patients only when the expected benefits clearly outweigh the potential risks to the fetus and mother.

Pediatric Use: The safety and efficacy of dobutamine for use in children have not been established.

Drug Interaction: Clinical 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.

No evidence of drug interactions were noted in clinical studies when dobutamine was administered concurrently with other drugs including digitalis preparations and/or furosemide, spironolactone, lidocaine, nitroglycerin, isosorbide dinitrate, morphine, atropine, anticoagulants and potassium chloride supplements.

ADVERSE REACTIONS

Cardiovascular: The most common adverse reactions relate to the effect of dobutamine on the cardiovascular system.

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

Hypotension: Precipitous decreases in blood pressure associated with dobutamine therapy have been reported. A reduction in dose or discontinuation of the drug is necessary to return the blood pressure to baseline levels. In some cases pressor support may be required.

Less commonly occurring effects related to the cardiovascular system include cardiac awareness, transient bigeminy, bradycardia, angina, palpitations, non-specific chest pain, and shortness of breath.

Gastrointestinal: Nausea, vomiting and bad taste.

Central Nervous System: Headache, anxiety, fatigue, and paresthesia.

Hypersensitivity: Rash, fever, eosinophilia and bronchospasm have been reported occasionally.

Miscellaneous Reactions: Dyspnea, thrombocytopenia, pruritis, chill, and sweating have been observed rarely. Phlebitis has been occasionally reported, as have been local inflammatory changes following inadvertent infiltration.

Administration of Dobutamine Injection USP, like other β_2-agonists has been associated with decreases in serum potassium concentrations, rarely to hypokalemic values.

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In case of overdosage, as evidenced by excessive blood pressure alteration or tachycardia, reduce the rate of administration, or temporarily discontinue Dobutamine Injection USP until the patient's condition stabilizes. Because dobutamine's duration of action is short, no additional remedial measures are usually necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Note: DOBUTAMINE INJECTION USP is a potent drug; it is not for direct injection and must be diluted exactly as directed before administration to patients as an intravenous infusion (see PRECAUTIONS).

Preparation and Stability: Dobutamine Injection USP is incompatible with alkaline solutions and should not be mixed with products such as 5% sodium bicarbonate injection. Because of the occurrences of physical incompatibilities with some drugs and the potential for

incompatibility with other drugs, 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 sodium bisulfite and ethanol. The diluted solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration. Discard any unused portion.

Dobutamine Injection USP must be diluted at the time of administration to at least 50 mL with either Dextrose 5% or Sodium Chloride 0.9% prior to administration by IV infusion. Intravenous solutions should be used within 24 hours of preparation.

Solutions containing dobutamine may exhibit a colour that, if present, will increase with time. This colour change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage: The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 µg/kg/min (see Table). Some patients may respond to doses as low as 0.5 µg/kg/min.; whereas, on rare occasions, infusion rates up to 40 µg/kg/min. have been required to obtain the desired effect.

Table 1: Rates of Infusion for Concentrations of 250, 500, and 1 000 mg/L

	Infusion Delivery Rate		
Drug Delivery Rate (µg/kg/min)	250 mg/L* (mL/kg/min)	500 mg/L** (mL/kg/min)	1000 mg/L*** (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 mg per liter of admixture
** 500 mg per liter or 250 mg per 500 mL of admixture
*** 1000 mg per liter or 250 mg per 250 mL of admixture

The final volume administered should be determined by the fluid requirements of the patient.

The rate of administration and 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.

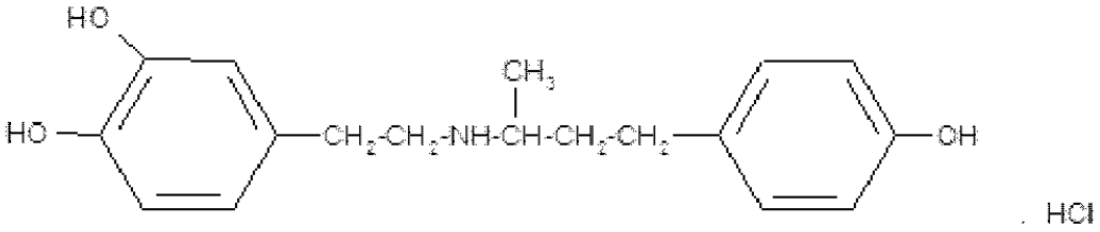
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Dobutamine hydrochloride

Chemical Name: (±)-4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl] amino]ethyl]-1,2-benzenediol hydrochloride.

Structural Formula:



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

Molecular Weight: 337.84 g/molDescription: White or almost white crystalline powder. Sparingly soluble in water and in methyl alcohol; soluble in ethyl alcohol and pyridine. Melting point of 198°C - 192°C.

Composition

Each mL of Dobutamine Injection USP contains: dobutamine 12.5 mg (as hydrochloride), sodium metabisulfite 0.15 mg, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

Stability and Storage Recommendations

Concentrated Solution

Store between 15 and 30 °C. Protect from light. Discard unused portion.

Diluted Solutions

Intravenous solutions diluted to at least 50 mL with either Dextrose 5% or Sodium Chloride 0.9% should be used within 24 hours of preparation when stored at 15-25°C. The diluted

solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration. Discard any unused portion.

AVAILABILITY OF DOSAGE FORMS

Dobutamine Injection USP is available in 20 mL single use ampoules, boxes of 10.

PHARMACOLOGY

Pharmacokinetics: In animal studies, peak plasma levels of dobutamine occurred within 8 to 10 minutes. In the dog, the plasma half-life of dobutamine is 1 to 2 minutes. The major circulating metabolites are glucuronides of 3-*o*-methyl dobutamine with a plasma half-life of 1.9 hours. Dobutamine and its metabolites are eliminated in the urine and bile. Plasma half-life of dobutamine in humans is 2 minutes. The major 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.

Hemodynamic Effects: Administered to healthy, conscious dogs at a dosage of 8 μg/kg/min. without blocking agents, dobutamine changed cardiac output and total peripheral resistance little because it tended to increase stroke volume slightly while simultaneously reducing heart rate. Arterial pressure remained constant. At doses of 20 to 40 μg/kg/min., cardiac output rose progressively and substantially from 2.41 (control) to 3.23 and 4.35 liter/minute respectively; the increases were accompanied by significant reductions in total peripheral resistance. The increase in cardiac output was due primarily to an increase in stroke volume (+ 33%) at the intermediate dose; at the high dose, it was due to increases in both heart rate (+ 33 beats/min.) and stroke volume (+ 42%). Mean arterial pressure increased minimally with increasing dosage.

Dobutamine is a direct-acting agonist, not taken up by adrenergic nerve fibers. It has strong β_1 inotropic activity, but exerts less effect on α and β_2 vascular receptors. Blockage with propranolol negates the inotropic effect, but fails to unmask additional pressor activity.

TOXICOLOGY

Acute Toxicity (IV):

Species	LD_{50}(mg/kg)
Mouse (F)	72.2 ± 3.7
Mouse (M)	69.0 ± 2.5
Rat (F)	84.1 ± 4.5
Rat (M)	94.0 ± 2.9

Prostration was noted immediately after injection in both species. Most deaths occurred during the first 4 minutes. Salivation in some of the surviving mice and hypoactivity in rats were observed.

Two dogs survived doses of 40mg/kg. Tachycardia, marked changes in EKG patterns, vasodilatation, and vomiting were noted.

Signs of toxicity in cats following doses of 40 mg/kg were vomiting, mydriasis, vasodilatation, and ataxia.

Subacute Toxicity: Increased heart rate and myocardial necrosis occurred in 1 of 20 rats surviving 10 mg/kg daily for 2 weeks.

Signs of toxicity in dogs following daily doses up to 6 mg/kg for 2 weeks were vomiting, marked tachycardia, increased respiration, vasodilatation, mydriasis, and occasional myoclonic jerking. One dog showed changes in EKG for the first 48 hours.

Dogs were given continuous intravenous infusion of dobutamine (in 5% dextrose) for 2 weeks at rates of 25, 50 and 100 µg/kg/min. The mid and high dose animals salivated

profusely; vasodilatation was observed during the first week and all dogs were anorexic. The dogs in the high dose group were depressed and lethargic for the first three days. Alkaline phosphatase and creatine phosphokinase values were elevated and serum potassium was decreased during the first week but returned to normal. The EKG patterns showed elevated amplitude of the T wave in 3 or 4 animals but the effect disappeared after a few hours and no ectopic beats were seen.

Dogs were given dobutamine by continuous infusion in gradually increasing rates up to 300 μg/kg/min. over a period of 4 days. Salivation occurred at 20 and 40 μg/kg/min. doses and peripheral dilation was seen at higher doses.

Teratology Studies: Rats were administered intravenous doses of 5, 10 and 15 mg/kg/day on gestation days 6 to 15. Rabbits received intravenous doses of 30 mg/kg on gestation days 6 through 18. Reproduction parameters were unaffected by treatment. No fetal drug related abnormalities were observed.

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