# PRODUCT MONOGRAPH

## [Pr]DOBUTREX®
**(Dobutamine, USP)**

**Solution for Injection**

**Sympathomimetic**

Pharmaceutical Partners of Canada Inc.
45 Vogell Road, Suite 200
Richmond Hill, ON L4B 3P6

Date of Preparation:
January 14, 2008

Control No.: 119232

**PRODUCT MONOGRAPH**
**DOBUTREX® SOLUTION**
**(Dobutamine Injection, USP)**
**Sympathomimetic**

## ACTION AND CLINICAL PHARMACOLOGY

DOBUTREX SOLUTION (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. It does not cause the release of endogenous norepinephrine as does dopamine. No specific effect on the renal vasculature was observed. In both animal and human studies dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

The onset of action is within one to two minutes, the peak effect of a particular infusion may not be reached for ten minutes. The plasma half-life in humans is two minutes.

## INDICATIONS AND CLINICAL USE

DOBUTREX SOLUTION (dobutamine) 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 DOBUTREX SOLUTION 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 base-line values.

## CONTRAINDICATIONS

DOBUTREX SOLUTION (dobutamine) is contraindicated in patients with pheochromocytoma, in patients with idiopathic hypertrophic subaortic stenosis, and in those patients with hypersensitivity to dobutamine.

## WARNINGS

DOBUTREX SOLUTION (dobutamine) may cause a marked increase in heart rate or blood pressure, especially systolic pressure. About 10 percent of patients in clinical studies have had rate increases of 30 beats per minute or more, while about 7.5 percent have had a 50 mmHg or greater increase in systolic pressure. Patients with preexisting

hypertension appear to have an increased risk of developing an exaggerated pressor response. Reduction of dosage usually reverses these effects promptly.

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

Reactions suggestive of hypersensitivity associated with administration of DOBUTREX SOLUTION, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally. DOBUTREX SOLUTION contains sodium bisulfite, 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 DOBUTREX SOLUTION. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response.

DOBUTREX SOLUTION 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 DOBUTREX SOLUTION stems from stimulation of cardiac $\beta_1$ receptors, this effect is, of course, prevented by β-blocking drugs.

## PRECAUTIONS

### General

During the administration of DOBUTREX SOLUTION (dobutamine), as with any adrenergic agent, EKG, heart rate and blood pressure should be continuously monitored. In addition, monitoring of pulmonary wedge pressure and cardiac output should be performed whenever possible to aid in the safe and effective infusion of DOBUTREX SOLUTION.

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

Hypovolemia should be corrected with suitable volume expanders before treatment with DOBUTREX SOLUTION.

DOBUTREX SOLUTION should be used with caution in patients with hyperthyroidism.

DOBUTREX SOLUTION should be used with caution in patients receiving anesthetic agents, cyclopropane, or halogenated hydrocarbons.

DOBUTREX SOLUTION should be used with caution in patients taking concomitantly other sympathomimetic amines.

DOBUTREX SOLUTION like other $\beta_2$-agonists can produce a mild reduction in serum potassium concentration (rarely to hypokalemic levels). Accordingly, consideration should be given to monitoring serum potassium.

**Usage Following Acute Myocardial Infarction**
Clinical experience with DOBUTREX SOLUTION 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 DOBUTREX SOLUTION. 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 DOBUTREX SOLUTION for use in children have not been established.

**Drug Interactions**
Clinical studies indicate that the concomitant use of DOBUTREX SOLUTION 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 DOBUTREX SOLUTION was administered concurrently with other drugs including digitalis preparations and/or furosemide, spironolactone, lidocaine, glyceryl trinitrate, 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 mmHg increase in systolic blood pressure and an increase in heart rate of five to fifteen beats per minute have been noted in most patients. (See **WARNINGS** regarding exaggerated chronotropic and pressor effects.) About 5 percent of patients

have had increased premature ventricular beats during infusions. These effects are 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 common**
Cardiac awareness, transient bigeminy, bradycardia, angina, non-specific chest pain, palpitations, 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 were observed rarely. Phlebitis has been occasionally reported. Local inflammatory changes following inadvertent infiltration.

Administration of DOBUTREX SOLUTION (dobutamine), like other catecholamines, 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.

## 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 DOBUTREX SOLUTION (dobutamine) until the patients condition stabilizes. Because the duration of action of DOBUTREX SOLUTION is short, no additional remedial measures are usually necessary.

## DOSAGE AND ADMINISTRATION

**Note:** **DOBUTREX SOLUTION (DOBUTAMINE) 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).**

DOBUTREX SOLUTION 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 DOBUTREX SOLUTION not be mixed with other drugs in the same solution. DOBUTREX SOLUTION should not be used in conjunction with other agents or diluents containing both sodium bisulfite and ethanol.

DOBUTREX SOLUTION must be further diluted at the time of administration to at least 50 mL prior to administration in an IV container with one of the following intravenous solutions: 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within twenty-four hours of preparation.

Solutions containing DOBUTREX 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.

**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)** | **1,000 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 diluent

** 500 mg per liter or 250 mg per 500 mL of diluent
*** 1,000 mg per liter or 250 mg per 250 mL of diluent

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

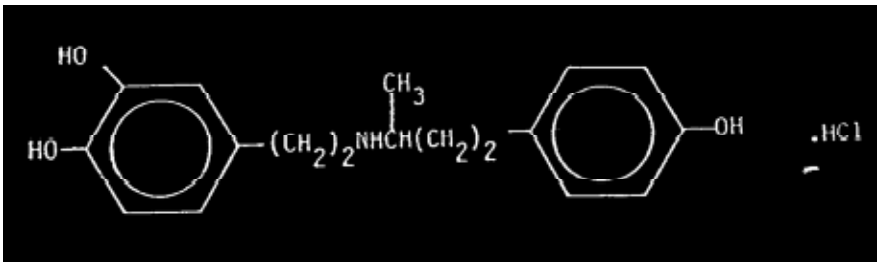
**Drug Substance:**

**Trade Name:** DOBUTREX SOLUTION

**Proper Name:** Dobutamine hydrochloride

**Chemical Name:** (±)-4-[2-[[3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-pyrocatechol hydrochloride

**Structural Formula:**




**Molecular Formula:** $C_{18}H_{23}NO_3HCl$

**Molecular Weight**: 337.84

**Composition:** Each mL DOBUTREX SOLUTION contains 12.5 mg dobutamine, 0.24 mg sodium bisulfite and water for injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

## STABILITY AND STORAGE RECOMMENDATIONS

DOBUTREX SOLUTION should be stored between 15 and 30°C.

## AVAILABIILITY OF DOSAGE FORMS

DOBUTREX SOLUTION 250 mg/20 mL VL 7175
Each vial contains 250 mg dobutamine, 4.8 mg sodium bisulfite and water for injection. To be used for intravenous infusion only. Must be diluted prior to use. Available in packages of 10 vials.

## PHARMACOLOGY

**Pharmacokinetics**

In animal studies, peak plasma levels of dobutamine occurred within eight to ten minutes. In the dog, the plasma half-life of dobutamine is one to two minutes. The major circulating metabolites are glucuronides of 3-0-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 two 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 3-0-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 percent) at the intermediate dose; at the high dose, it was due to increases in both heart rate (+33 beats/min) and stroke volume (+42 percent). Mean arterial pressure increased minimally with increasing dosage.

Dobutamine is a direct-acting agonist, not taken up be adrenergic nerve fibers. It has strong $\beta_1$ inotropic activity, but exerts less effect on α and $\beta_2$ vascular receptors. Blockade 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 four minutes. Salivation in some of the surviving mice and hypoactivity in rats were observed.

Two dogs survived doses of 40 mg/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 one of twenty rats surviving 10 mg/kg daily for two weeks.

Signs of toxicity in dogs following daily doses up to 6 mg/kg for two weeks were vomiting, marked tachycardia, increased respiration, vasodilatation, mydriasis, and occasional myoclonic jerking. One dog showed changes in EKG for the first forty-eight 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 anorectic. 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 of 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 four 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 to 18. Reproductive parameters were unaffected by treatment. No fetal drug related abnormalities were observed.

**BIBLIOGRAPHY**

*Animal Studies:*


1. Bolter, C.P., and Ledsome, J.R.: Inotropic and chronotropic responses of the *in-vitro* denervated dog myocardium to dobutamine, Canad. J. Physiol. Pharmacol., 1976, 54: 618-621.

2. Clayman, M.D., et. al.: Hypokalemia associated with dobutamine administration, Kidney International, 1989, 35:215.

3. Driscoll, D.J., Lewis, R.L., Hartley, C.J., Gillette, P.C., and Schwartz, A: Cardiovascular responses of neonatal canine to dopamine, dobutamine and isoproterenol, Pediat. Res., 1977, 11/4:389.

4. Goldenberg, I.F., et. al.: Effect of dobutamine on plasma potassium in congestive heart failure secondary to idiopathic or ischemic cardiomyopathy, Am. J. Cardiol., 1989, 63:843-846.

5. Hinds, J.E., and Hawthorne, E.W.: Comparative Cardiac Dynamic Effects of Dobutamine and Isoproterenol in Conscious Instrumented Dogs, Am. J. Cardiol., 1975, 36:894.

6. Holloway, G.A., Jr., and Frederickson, E.L.: Dobutamine, a New Beta Agonist, Anesth. Analg. Curr. Res., 1974, 53:616.

7. Murphy, P.J., Williams, T.L., and Kau, D.L.K.: Disposition of dobutamine in the dog, J. Pharmacol. Exp. Ther., 1976, 199:423.

8. Robie, N.W., Nutter, D.O., Moody, C., and McNay, J.L.: *In-vivo* analysis of adrenergic receptor activity of dobutamine, Circ. Res., 1974, 34:663.

9. Tuttle, R.R., and Mills, J.: Dobutamine: Development of a new catecholamine to selectively increase cardiac contractility, Circ. Res., 1975, 36:185.

10. Tuttle, R.R., Pollock, G.D., Todd, G., MacDonald, B., Tust, R., and Dusenberry, W.: The effect of dobutamine on cardiac oxygen balance, Regional Blood Flow and Infarction Severity After Coronary Artery Narrowing in Dogs, Circ. Res. (In press).

11. Vatner, S.F., McRitchie, R.J., and Braunwald, E.: Effects of dobutamine on left ventricular performance, coronary dynamics, and distribution of cardiac output in conscious dogs, J. Clin. Invest., 1974, 53:1265.

12. Willerson, J.T., Hutton, I., Watson, J.T., Platt, M.R., and Templeton, G.H.: Influence of dobutamine on regional myocardial blood flow and ventricular performance during acute and chronic myocardial ischemia in dogs, Circulation, 1976, 55:828.

*Clinical Studies:*


1. Akhtar, N., Mikulic, E., Cohm, J.N., and Chaudhry, M.H.: Hemodynamic effect of dobutamine in patients with severe heart failure, Am. J. Cardiol., 1975, 36:202.

2. Beregovich, J., Bianchi, C., D'Angelo, R., Diaz, R., and Rubler, S.: Haemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure, Br. Heart J., 1975, 37:629.

3. Berkowitz, C., Croke, R., Jacobs, W., Loeb, H., and Gunnar, R.: Comparative responses to dobutamine and nitroprusside in patients, Amer. J. Cardiol., 1977, 39/2:297.

4. Bianchi, C., Diaz, R., Gonzales, C., and Beregovich, J.:Effects of Dobutamine on Atrioventricular Conduction, Am. Heart J., 1975, 90:474.

5. Braunwald, E., McRitchie, R.J., and Vatner, S.F.: Effects of anesthesia and the open chest on myocardiac responses to sympathomimetic amines, Fed. Proc., 1974, 33; 517, (Abstract).

6. Bush, C.A., Webel, J., Leier, C.V.: Treatment of end stage cardiac failure with dobutamine, Amer. J. Cardiol., 1976, 37/1:125.

7. Delius, W., Wirtzfeld, A., Sebening, H., and Mathes, P.: Hemodynamic effect of dobutamine in patients with cardiac insufficiency, Dtsch. Med. Wschr., 1976, 101:1747-1751.

8. Fuchs, R.M., Ruglen, D.L., and Powell, W.J.: Effects of dobutamine on venous capacity, Clin. Res.,1976, 24/3:A218.

9. Gauthier, J.P., Haberer, J.P., Zimmer, R.: Cardiovascular Effects of dobutamine-comparative study – first results in an intensive-care unit, Anesth. Analg. Reanim., 1976, 33/3:375-389.

10. Gillespie, T.A., Roberts, R., Dieter, A., and Sobel, B.E.: Salutary effects of dobutamine on hemodynamics without exacerbation of arrhythmia of myocardial injury, Circulation, 1975, 52:76.

11. Gillespie, T.A., Ambos, H.D. Sobel, B.E., and Roberts, R.: Effects of dobutamine in patients with acture myocardial infarction, Amer. J. Cardiol., 1977, 39/4:588-594.

12. Goldberg, L.T., Hsieh, Y.Y., and Resnekov, L: Newer Catecholamines for treatment of heart failure and shock – Update on dopamine and a first look at dobutamine, Prog. Card., 1977, 19/4:327-340.

13. Jewitt, D., Mitchell, A., Birkheard, J., and Dollery, C.: Clinical cardiovascular pharmacology of dobutamine, A selective inotropic catecholamine, Lancet, 1974, p. 363.

14. Kersting, F., Follath, F., Moulds, R., Mucklow, J., McCloy, R., Sheares, J., and Dollery, C.: A comparison of cardiovascular effects of dobutamine and isoprenaline after open-heart surgery, Brit. Heart J., 1976, 38:622.

15. Leier, C.V., Webel, J., and Bush, C.A.: Clinical pharmacology of dobutamine, Clin. Res., 1976, 24/3:511.

16. Leier, C.V., Webel. J., and Bush, C.A.: The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure Circulation, 1977, 56/3:468-472.

17. Leighton, K.M., and Bruce, C.: Dobutamine and general anesthesia – Study of response of arterial pressure, heart rate and renal blood flow, Canad. Anaesth. Soc. J., 1976, 23/2:176.

18. Loeb, H.S., Khan, M., Klodnycky, M.L., Sinno, M.Z., Towne, W.D., and Gunnar, R.M.: Hemodynamic effects of dobutamine in man, Circ. Shock, 1975, 2:29.

19. Loeb, H.S., Sinno, M.Z., Saudye, A., Towne, W.D., and Gunnar, R.M.: Electrophysiologic properties of dobutamine, Circ. Shock, 1974, 1:217.

20. Loeb, H.S., Khan, M., Saudye, A., and Gunnar, R.M.: Acute hemodynamic effects of dobutamine and isoproterenol in patients with low output cardiac failure, Circ., Shock, 1976, 3:55.

21. Loeb, H.S., Bredakis, J., and Gunnar, R.M.: Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure, Circulation, 1977, 55:375-381.

22. Meyer, S.L., Curry, G.C., Donsky, M.S., Twieg, D.B., Parkey, R.W., and Willerson, J.T.: Influence of dobutamine on hemodynamics and coronary blood flow in patients with and without coronary artery disease, Amer. J. Cardiology, 1976, 38:103.

23. Robie, N.W., and Goldberg, L.I.: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine, Am. Heart J., 1975, 90:340.

24. Sakamoto, T., and Yamada, T.: Hemodynamic effects of dobutamine in patients following open heart surgery, Circulation, 1977, 55/3:525-533.

25. Tinker, J.H., Tarhan, S., White, R.D., Pluth, J.R., and Barnhorst, D.A.: Dobutamine for inotropic support during emergence from cardiopulmonary bypass, J. Anesthesiol., 1976, 44:281.