# Inotrop
## Dobutamine HCL 25 mg/mL
CONCENTRATE FOR SOLUTION FOR INFUSION

**NAME OF THE MEDICINAL PRODUCT**
Inotrop (Dobutamine HCL 25 mg/ml Concentrate for Solution for Infusion)

**COMPOSITION**
Each mL contains :
Dobutamine hydrochloride equivalent to Dobutamine 25 mg
Each vial of 10 mL contains a total of Dobutamine Hydrochloride equivalent to Dobutamine 250 mg

**PRODUCT DESCRIPTION**
Clear, colorless to slightly yellowish, odorless solution, free from visible dirt, packaged in 10R clear DIN vial, 20-mm red ready to sterilized rubber stopper, 20-mm green flip off
Description after dilution (with NaCl 0.9% solution for infusion, Dextrose 5% for infusion and Ringer lactate solution for infusion) : Clear, colorless to slightly yellowish, odorless solution, free from visible dirt.
The product is not supplied with the diluents

**PHARMACOLOGY**
***Pharmacodynamics***
Inotrop (Dobutamine hydrochloride Injection) 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 hydrochloride produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.
***Pharmacokinetics***
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 usually not accompanied by marked increases in heart rate and cardiac stroke volume is usually increased.
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.
The onset of action of Inotrop 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 cathechol and conjugation.
In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative is inactive.

**INDICATIONS**
Dobutamine Hydrochloride Injection is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decomposition 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 hydrochloride.

**DOSAGE AND METHOD OF ADMINISTRATION**
Note – Do not add Dobutamine Hydrochloride 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.

Reconstitution and Stability – At the time of administration, Dobutamine Hydrochloride Injection must be further diluted in an I.V. container to at least a 50-mL solution using 1 of the following intravenous solutions as a diluent: 5% Dextrose Injection, 0.9% Sodium Chloride Injection and Lactated Ringer's Injection. Intravenous solutions should be used within 24 hours.

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

Recommended Dosage – The rate of infusion needed to increase cardiac output usually ranged from 2.5 to 15 µg/kg/min (see table). On rare occasions, infusion rates up to 40 µ g/kg/min have been required to obtain the desired effect.

Rate of infusion for Concentrations of 250, 500 and 1,000 mcg/ml
Infusion Delivery Rate:

| Drug Delivery Rate | 250 mcg/mL* | 500 mcg/mL† | 1000 mcg/mL‡ |
|---|---|---|---|
| µg/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.

Rate of Administration - When administering dobutamine hydrochloride (or any potent medication) by continuous intravenous infusion, it is advisable to use a precision volume control I.V. set.

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 of up to 5,000 mcg/L 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.

**ROUTE OF ADMINISTRATION**
Intravenous (IV)

**CONTRAINDICATIONS**
- Patients with idiopathic hypertrophic subaortic stenosis.
- Patients who have shown previous manifestation of hypersensitivity to dobutamine hydrochloride.

**WARNINGS AND PRECAUTIONS**
**PRECAUTIONS:** During the administration of Dobutamine Hydrochloride, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary artery wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutamine Hydrochloride.
Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutamine Hydrochloride is instituted.
In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutamine Hydrochloride.
Dobutamine Hydrochloride may be ineffective if the patientts has recently received a beta blocking drug. In such a case, the peripheral vascular resistance may increase. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.
There is concern that any agent which increases contractile force and heart rate may increase the size of an infraction by intensifying ischaemia, but it is not known whether dobutamine does so in man.
**Pediatric Use:** The safety and efficacy of Dobutamine Hydrochloride for use in children have not been studied.
**Usage in Hypotension:** When hypotension is largely attributable to decreased cardiac output and coincides with an elevated ventricular filling pressure, the infusion of dobutamine HCL may help to restore the pressure.
As volume is replenished in the treatment of acute hypoperfusion states and there is an increase in pulmonary wedge or central venous pressure but with no increase in cardiac output and arterial pressure, dobutamine may improve output and help restore the arterial pressure.
In general, when mean arterial blood pressure is 70 mmHg in the absence of an increased ventricular filling pressure, hypovolemia may be present and would require treatment with appropriate volume repleting solution before dobutamine HCL is given.
If arterial blood pressure remains low or decreases progressively during administration of dobutamine HCL despite adequate ventricular filling pressure and cardiac output, consideration may be given to the concomitant use of a peripheral vasoconstrictor agent, e.g. dopamine or norepinephrine.
Reactions at Site of Intravenous Infusion: Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration. Isolated cases of cutaneous necrosis have been reported.

**WARNINGS:**
**Increase in Heart Rate or Blood Pressure:** Dobutamine Hydrochloride may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients have had rate increases of 30 beats/minute or more , and about 7.5 percent have a 50 mmHg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing an exaggerated pressor response.
**Ectopic Activity:** Dobutamine Hydrochloride may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.
**Anaesthetics:** The myocardium may be sensitized to the effect of dobutamine by cyclopropane or halogenated hydrocarbon anaesthetics, and these should be avoided.

**Warning for Sodium Metabisulphite:** This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.

**DRUG INTERACTIONS**
***Halogenated anaesthetics:***
Although it is less likely than adrenaline to cause ventricular arrhythmias, Dobutamine 25 mg/ml concentrate for solution for infusion should be used with great caution during anaesthesia with cycloproprane, halothane and other halogenated anaesthetics.
***Entacapone:***
The effects of Dobutamine 25 mg/ml concentrate for solution for infusion may be enhanced by entacapone.
***Beta-blockers:***
The inotropic effect of dobutamine stems from stimulation of cardiac beta1 receptors, this effect is reversed by concomitant administration of beta-blockers. Dobutamine has been shown to counteract the effect of beta-blocking drugs. In therapeutic doses, dobutamine has mild alpha1- and beta2-agonist properties. Concurrent administration of a non-selective beta-blocker such as propranolol can result in elevated blood pressure, due to alpha-mediated vasoconstriction, and reflex bradycardia. Beta-blockers that also have alpha-blocking effects, such as carvedilol, may cause hypotension during concomitant use of dobutamine due to vasodilation caused by beta2 predominance.

**FERTILITY, PREGNANCY AND LACTATION**
Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility, harm to the foetus, or teratogenic effects due to dobutamine. As there are no adequate and well-controlled studies in pregnant women, and as animal reproduction studies are not always predictive of human response, dobutamine should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.

**SIDE EFFECTS**

**Adult population**

Infusions for up to 72 hours have revealed no adverse effects other than those seen with shorter infusions. There is evidence that partial tolerance develops with continuous infusions of Dobutamine 25 mg/ml concentrate for solution for infusion for 72 hours or more; therefore, higher doses may be required to maintain the same effects.

Immune system disorders:
Not Known: Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to sulfite sensitivity

Blood and lymphatic system disorders
Common: Eosinophilia, inhibition of thrombocyte aggregation (only when continuing infusion over a number of days)

Metabolism and nutrition disorders
Very rare: Hypokalaemia

Nervous system disorders
Common: Headache
Not known: Paraesthesia, tremor, myoclonic spasm. Myoclonus has been reported in patients with severe renal failure receiving dobutamine;

Cardiac disorders/vascular disorders
Very common: Increase of the heart rate by ≥ 30 beats/min
Common: Blood pressure increase of ≥ 50 mmHg. Patients suffering from arterial hypertension are more likely to have a higher blood pressure increase; Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles.; Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised prior to dobutamine infusion.; Vasoconstriction in particular in patients who have previously been treated with beta receptor blockers.; Anginal pain, palpitations
Uncommon: Ventricular tachycardia, ventricular fibrillation
Very rare: Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest
Not known: Electrocardiogram ST segment elevation; Decrease in pulmonary capillary pressure
Eosinophilic myocarditis has been noted in explanted hearts of patients who had undergone treatment with multiple medications including dobutamine or other inotropic agents prior to transplantation.
Children: pronounced increase of heart rate and/or blood pressure as well as a lower decrease of the pulmonary capillary pressure than adults. Increase of pulmonary capillary pressure in children under 1.

Gastrointestinal disorders
Not known: Nausea,

Psychiatric disorders
Not known: Restlessness, feeling of heat and anxiety

Renal and urinary disorders
Not known: Urinary urgency;

**SYMPTOMS AND TREATMENT OF OVERDOSE**

Overdoses of dobutamine have been reported rarely. The following is provided to serve as a guide if such an overdose is encountered.
**Symptoms:** Toxicity from Dobutamine HCL is usually due to excessive cardiac β-receptor stimulation. The duration of action of dobutamine HCL is generally short (T1/2 = 2 min) because it is rapidly metabolised 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.
If the product is ingested, unpredictable absorption may occur from the mouth and the gastrointestinal tract.
**Treatment:** In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in the patient. The initial actions to be taken in a dobutamine hydrochloride 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. Absorption of drugs from 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, haemodialysis or charcoal hemoperfusion have not been established as beneficial for an overdose of dobutamine hydrochloride.

**INCOMPATIBILITIES**

Do not add Dobutamine 25 mg/ml concentrate for solution for infusion to 5% Sodium Bicarbonate intravenous infusion BP or to any other strongly alkaline solutions. Because of potential physical incompatibilities, it is recommended that dobutamine hydrochloride not be mixed with other drugs in the same solution.

Dobutamine 25 mg/ml concentrate for solution for infusion should not be used with other agents or diluents containing both sodium metabisulfite and ethanol.

**SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**

Dobutamine Concentrated should be diluted before use and administered by IV infusion only.
The final concentrations generally used for infusion are 250 mcg/mL, 500 mcg/mL or 1000 mcg/mL (see table in Dosage for infusion delivery system).

The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride 0.9% (9 mg/mL), dextrose solution 5% (50 mg/mL), or Ringer lactate solution.

Solutions of dobutamine hydrochloride may have a pink discolouration. This discolouration, which will increase with time, results from a slight oxidation of the drug. However, there is no significant loss of drug potency within the recommended maximum in-use storage time of 24 hours at temperature below 30ºC.

**STORAGE**

Store below 30ºC
Infusion must be aseptically prepared.
After dilution with compatible infusion solution such as: 0.9% sodium chloride, 5% dextrose and ringer lactate, the solution is stable up to 24 hours at temperature below 30ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

**PRESENTATION**

Box contains 2 x 10 mL vials

**NATURE AND CONTENTS OF CONTAINER**

10R Clear Glass vial. Packed in Duplex Carton to contain 2 vials x 10 ml

Reg. No. :
Indonesia : DKL9531510243A1
Malaysia : MAL.....

**ON MEDICAL PRESCRIPTION ONLY**

**KEEP MEDICINE OUT OF REACH OF CHILDREN**

Manufactured by :
**PT. PRATAPA NIRMALA**
Jl. Industri VI, Tangerang Banten 15135,
Kec. Jatiuwung, Kota Tangerang, Banten, Indonesia

FAHRENHEIT
PT. PRATAPA NIRMALA

Revision Date : 20 May 2022