DBL™ Dobutamine Hydrochloride Injection
(Dobutamine hydrochloride)

1. NAME OF THE MEDICINE
Dobutamine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 20 mL vial of DBL Dobutamine Hydrochloride Injection contains dobutamine hydrochloride 280.2 mg (250 mg dobutamine equivalent) and sodium metabisulfite 4.4 mg.

Dobutamine hydrochloride is a white to practically white, crystalline powder. It is sparingly soluble in water and methyl alcohol; soluble in alcohol.

Excipient with known effect:
- Sodium Metabisulfite

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Solution for injection.
DBL Dobutamine Hydrochloride Injection is a sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
DBL Dobutamine Hydrochloride Injection is indicated in adults who require short-term treatment of cardiac failure secondary to acute myocardial infarction, or cardiac surgery.

4.2 Dose and method of administration
Dosage
The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 micrograms/kg/min (see table). On rare occasions, infusion rates up to 40 micrograms/kg/min have been required to obtain the desired effect. However, the possibility of intensifying myocardial ischaemia should be borne in mind and the lowest effective dose infused.

Rates of infusion for concentrations of 250, 500 and 1,000 micrograms/mL

Drug Delivery Rate (microgram/kg/min)	Infusion Delivery Rate		
	250 microgram/mL[1] (mL/kg/min)	500 microgram/mL[2] (mL/kg/min)	1000 microgram/mL[3] (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

[1.] 250 mg per litre of diluent
[2.] 500 mg per litre or 250 mg per 500 mL of diluent
[3.] 1000 mg per litre or 250 mg per 250 mL of diluent.

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 up to 5000 micrograms/mL have been administered to humans (250 mg/50 mL). The final volume administered should be determined by the fluid requirements of the patient.

Method of administration
DBL Dobutamine Hydrochloride Injection must be diluted to at least 50 mL at the time of administration in 5% Glucose Injection or 0.9% Sodium Chloride Injection. Although chemically stable for 24 hours, prepared solutions should be used immediately after dilution.

Do not add DBL Dobutamine Hydrochloride Injection to 5% Sodium Bicarbonate Injection or any other strongly alkaline solutions. Dobutamine hydrochloride should not be used in conjunction with other agents or diluents containing sodium bisulfite.

4.3 Contraindications
DBL Dobutamine Hydrochloride Injection is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and previous hypersensitivity to dobutamine or any of the excipients.

Mechanical obstruction affecting left ventricular filling or outflow, especially in the case of obstructive cardiomyopathy or constrictive pericarditis.

4.4 Special warnings and precautions for use
Increase in heart rate or blood pressure
Dobutamine may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50 mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Patients with pre-existing hypertension appear to face an increased risk of developing an exaggerated pressor response.

Increased Atrioventricular Conduction
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 instituting therapy with dobutamine.

Ectopic activity
Dobutamine may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia. It is recommended that precautions be taken in patients with a history of severe ventricular arrhythmia.

Impaired Ventricular Filling and Ventricular Outflow Obstruction
Inotropic agents, including dobutamine, do not improve haemodynamics in most patients with mechanical obstruction that hinders either ventricular filling or outflow, or both. Inotropic response may be inadequate in patients with markedly reduced ventricular compliance. Such conditions are present in cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis. Minimal vasoconstriction has occasionally been observed, most notably in patients recently treated with a β-blocking drug.

Anaesthetics
The myocardium may be sensitised to the effect of dobutamine by cyclopropane or halogenated hydrocarbon anaesthetics, and these should be avoided.

Hypersensitivity
Reactions suggestive of hypersensitivity associated with the administration of dobutamine,

including skin rash, fever, eosinophilia and bronchospasm, have been reported occasionally.

DBL Dobutamine Hydrochloride Injection solution contains sodium metabisulfite, which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people.

Usage for Heart Failure Complicating an Acute Myocardial Infarction
Although the treatment of heart failure and the reduction in cardiac diameter will decrease myocardial oxygen consumption, there is still concern that the use of any positive inotropic agent may increase myocardial oxygen demand and the size of an infarction by intensifying ischaemia. Pertinent clinical data with dobutamine following acute myocardial infarction are limited but suggest that dobutamine does not have an adverse effect on the myocardium when used in doses that do not cause excessive increments in heart rate or arterial pressure. The dose of dobutamine should be titrated to prevent an excessive increase in heart rate and systolic blood pressure.

Animal studies have shown that massive doses of 30 mg/kg/min infused for 72 hours have produced irreversible myocardial damage.

General
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.

Hypovolaemia should be corrected with suitable volume expanders before treatment with dobutamine is instituted.

Because positive inotropic therapy can be associated with increases in intrapulmonary shunting, attention to arterial blood gases during treatment with dobutamine is recommended.

Dobutamine, like other beta-agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.

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 base-line values, but intervention may be required and reversibility may not be immediate.

Use in the elderly
No data available.

Paediatric use
The safety and efficacy of DBL Dobutamine Hydrochloride Injection for use in children have not been studied.

Effects on laboratory tests
No abnormal laboratory values attributable to dobutamine have been observed.

4.5 Interactions with other medicines and other forms of interactions
The potency of dobutamine may be decreased if the patient is given beta-adrenergic receptor antagonists. In such a case, the unopposed alpha-agonist effects of dobutamine may become apparent, including peripheral vasoconstriction and hypertension. Conversely, alpha-adrenergic blockade may make the beta1- and beta2-effects apparent, resulting in tachycardia

and vasodilatation.

There was no evidence of interactions with other medicines in clinical studies in which dobutamine was administered concurrently with the following medicines; digitalis preparations, frusemide, spironolactone, lignocaine, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid and paracetamol.

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 medicine is used alone.

Studies on limited numbers of patients with heart failure demonstrate that the combination of dobutamine and glyceryl trinitrate results in a lower pulmonary wedge pressure than when dobutamine is used alone and a higher cardiac output than when glyceryl trinitrate is used alone.

Beta blocker therapy, cyclopropane or halogenated hydrocarbon anaesthetics.

The effects of DBL Dobutamine Hydrochloride Injection may be enhanced by entacapone.

4.6 Fertility, pregnancy and lactation
Effects on fertility
No data available

Use in pregnancy – Category B2
Since there are no adequate and well-controlled studies in pregnant women, and since animal reproduction studies are not always predictive of human response, dobutamine hydrochloride should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.

Use in lactation
It is not known if dobutamine is distributed into breast milk. The decision of whether or not to treat lactating women with dobutamine should take into account the potential harmful effects to the infant. Should it be necessary to administer dobutamine to nursing mothers, breastfeeding should be suspended during the period of exposure.

4.7 Effects on ability to drive and use machines
The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Adverse effects (undesirable effects)
Many of the adverse effects of dobutamine are a quantitative extension of the pharmacological actions. The following adverse effects have been reported.

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 per minute have been noted in most patients (see section 4.4 Special Warnings and Precautions for Use regarding exaggerated chronotropic and pressure effects). Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related and their occurrence may require that the dose be reduced.

Electrocardiogram ST segment elevation has also been observed.

Cardiac disorders: Myocardial rupture, myocardial ischemia, eosinophilic myocarditis ventricular fibrillation ventricular tachycardia, angina pectoris, arteriospasm coronary, Stress

cardiomyopathy, arrhythmia, ventricular dysfunction tachycardia, ventricular extrasystoles, palpitations.

Respiratory, thoracic and mediastinal disorders: Dyspnea

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.

Miscellaneous uncommon effects: The following adverse effects have been reported in 1 to 3 percent 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 hypokalaemic levels (see section 4.4 Special Warnings and Precautions).

Immune system disorders: hypersensitivity reactions including rash, pruritus of the scalp, fever, eosinophilia, anaphylactic shock and bronchospasm.

Reaction 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.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose
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 beta-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short ($T_{1/2}$ = 2 minutes) 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
Because the duration of action of dobutamine is short, reducing the rate of administration or temporarily discontinuing dobutamine therapy until the patients condition stabilises is usually adequate. However, 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 an airway, and ensuring oxygenation and ventilation. Resuscitative

measures should be initiated promptly. Severe ventricular tachyarrhythmias may be successfully treated with propranolol or lignocaine. 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 the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage. 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 hydrochloride.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Dobutamine hydrochloride is an inotropic agent whose primary activity results from stimulation of the beta receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic and vasodilative effects. The drug is believed to be a direct agonist which, in animal studies, produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoprenaline.

In patients with depressed cardiac function, both dobutamine and isoprenaline 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, isoprenaline 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 in normal subjects and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimal vasoconstriction has been observed.

The onset of action is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

Clinical trials

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 base-line values. Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

5.2 Pharmacokinetic properties

Metabolism

The plasma half-life of dobutamine in humans is two minutes. The major routes of metabolism are methylation of the catechol and conjugation.

Excretion

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.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity
No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite
Water for injections

6.2 Incompatibilities

Dobutamine is incompatible with alkaline solutions such as sodium bicarbonate 5%.
Do not add DBL Dobutamine Hydrochloride Injection to 5% Sodium Bicarbonate Injection or any other strongly alkaline solutions. Dobutamine hydrochloride should not be used in conjunction with other agents or diluents containing sodium bisulfite.

6.3 Shelf life

Please refer to outer carton for expiry date.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

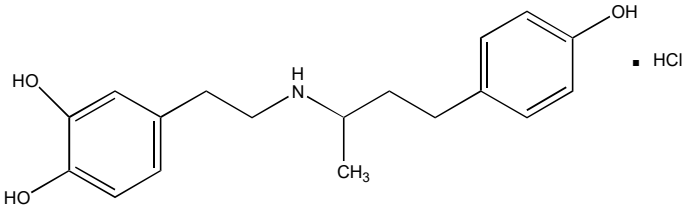
Compatibilities
DBL Dobutamine Hydrochloride Injection when diluted to 250 micrograms/mL and 500 micrograms/mL with 0.9% Sodium Chloride Injection and 5% Glucose Injection, was found to be stable for 24 hours at room temperature and in the presence of fluorescent light.

6.5 Nature and contents of container

DBL Dobutamine Hydrochloride Injection (250 mg/20 mL) is available in single vial.

6.6 Physicochemical properties

Chemical structure



Chemical name: (*RS*)-4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]-ethyl] benzene-1,2-diol hydrochloride
Molecular formula: $C_{18}H_{25}NO_3.HCl$
Molecular weight: 337.9

CAS number
49745-95-1

Pfizer Corporation Hong Kong Limited
MAR 2023
Version approved: 15 DEC 2023