SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

DOBUFAST

Dobutamine Injection USP

Strength:

50 mg/ml- 5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Sr. No.	Particulars	Grade	Qty./ml	Function
1.	Dobutamine Hydrochloride	USP	50 mg	Active

For the list of excipients , see section 6.1

3. PHARMACEUTICAL FORM:

Solution for Injection

A clear, colourless to pale straw colored solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Dobutamine injection 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.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with dobutamine hydrochloride.

4.2 Posology and method of administration:

Route of Administration: For I.V. Infusion after dilution only.

Note : Do not add Dobutamine Injection to 5% w/v 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 bisulfate and ethanol.

Preparation and Stability : At the time of administration, dobutamine injection must be further diluted in an IV container. Dilute 20 mL of dobutamine in at least 50 mL of diluent and dilute 40 mL of dobutamine in at least 100 mL of diluent. Use one of the following intravenous solutions as a diluent: Dextrose Injection 5%w/v, Dextrose 5%w/v and Sodium Chloride 0.45%w/v Injection, Dextrose 5%w/v and Sodium Chloride 0.9%w/v Injection, Dextrose Injection 10%w/v, Lactated Ringer's Injection, 5%w/v Dextrose in Lactated Ringer's Injection, Sodium Chloride Injection 0.9%w/v, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Recommended Dosage: The rate of infusion needed to increase cardiac output usually

ranged from 2.5 mcg/kg/min to 15 mcg/kg/min. On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Dobutamine Injection Rates of Infusion for Concentrations of 250, 500, and 1,000 mcg/mL

Drug Delivery Rate	Infusion Delivery Rate		
	250 mcg/mL*	500 mcg/mL†	1,000 mcg/mL‡
(mcg/kg/min)	(mcg/kg/min)	(mcg/kg/min)	(mcg/kg/min)
2.5	0.01	0.005	0.0025
5.0	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10.0	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15.0	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			

4.3 Contraindications:

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

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% of 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.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 injection, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.
Dobutamine injection 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 sulfites sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

1. During the administration of dobutamine injection, 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 hydrochloride.
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 : With reference to literature data Clinical experience with dobutamine injection following myocardial infarction has been insufficient to establish the safety of the drug for this use.

Laboratory Tests : Dobutamine, like other ß2- agonists, can produce a mild reduction in serum potassium concentration, rarely to hypokalemic levels. Accordingly, consideration should be given to monitoring serum potassium.

Pregnancy-Teratogenic Effects-Pregnancy Category B : This drug should be used during pregnancy only if clearly needed.

Nursing Mothers : If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

Pediatric Use: The safety and effectiveness of dobutamine injection for use in pediatric patients have not been studied.

Geriatric Use: 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.

4.5 Interaction with other medicinal products and other forms of interaction:

With reference literature, animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-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, nitroglycerin, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen.

4.6 Fertility, pregnancy and lactation:

Pregnancy-Teratogenic Effects-Pregnancy Category B : This drug should be used during pregnancy only if clearly needed.
Nursing Mothers : If a mother requires dobutamine treatment, breastfeeding should be discontinued for the duration of the treatment.

4.7 Effects on ability to drive and use machines:
Not Known.

4.8 Undesirable effects:
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. 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.
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.

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

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 β-receptor stimulation. The duration of action of dobutamine hydrochloride is generally short (T½ = 2bminutes) because it is rapidly metabolized by catechol-0-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 : 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.

5. PHARMACOLOGICAL PROPERTIES:

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. With reference literature, 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.

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Adrenergic and dopaminergic agents
ATC Code: C01CA07
Dobutamine is a synthetic, sympathomimetic amine, structurally related to isoproterenol and dopamine, and is administered as racemate. The positive inotropic effect is primarily based on the agonistic effect on cardiac beta1-receptors but also on cardiac alpha1-receptors; which leads to increased contractility with an increase in stroke volume. and cardiac output. Dobutamine also has an agonistic effect on peripheral beta2- receptors and to a smaller extent on peripheral alpha2-receptors. In accordance with the pharmacological profile, positive chronotropic effects occur as well as effects on the peripheral vascular system. These however, are less pronounced than the effects of other catecholamines. The haemodynamic effects are dose-dependent. The cardiac output increases primarily due to an increase in the stroke volume; an increase in the heart rate is observed particularly with higher dosages. There is a reduction in left ventricular filling pressure and systemic vascular resistance. With higher doses, there is also a reduction in the pulmonary resistance. Occasionally an insignificant increase of the systemic vascular resistance can be observed.
The volume increase due to an increase of the cardiac output is thought to be the reason for the blood pressure elevation. Dobutamine acts directly, independent from synaptic catecholamine concentrations, does not act at the dopamine receptor site, and – unlike dopamine – has no impact on the release of endogenous noradrenaline(norepinephrine).
There is a decrease of recovery time of sinus node and the A-V conduction time. Dobutamine may cause a tendency towards arrhythmia. When administered non-stop for more than 72 hours, tolerance phenomena were observed.
Dobutamine impacts the functions of thrombocytes. Like all other inotropic substances, dobutamine increases myocardial oxygen demand. Via reduction of the pulmonary vascular resistance and the hyperperfusion even of hypoventilated alveolar areas (formation of a pulmonary “Shunt”) a relatively reduced oxygen supply may occur in some cases. The increase in cardiac output and the resulting increase in coronary blood flow usually compensate these effects and cause – compared with other positive inotropic substances – a favourable oxygen supply/demand ratio.
Dobutamine is indicated for patients who require positive inotropic support in the treatment of cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures, especially when a low cardiac output is associated with raised pulmonary capillary pressure.
In cases of heart failure accompanied by acute or chronic myocardial ischaemia,

administration should be performed in a manner to prevent considerable increase in heart rate or blood pressure; otherwise, particularly in patients with a relatively good ventricular function, increase of ischaemia cannot be excluded.
There are only limited data with regard to clinical outcome including long-term morbidity and mortality. So far, no data exists to support a beneficial long-term effect on morbidity and mortality.
Dobutamine has no direct dopaminergic effect on renal perfusion.

Paediatric population

Dobutamine also exhibits inotropic effects in children, but the haemodynamic response Is somewhat different than that in adults. Although cardiac output increases in children, there is a tendency for systemic vascular resistance and ventricular filling pressure to decrease less and for the heart rate and arterial blood pressure to increase more in children than in adults. Pulmonary wedge pressure may increase during infusion of dobutamine in children 12 months of age or younger.
Increases in cardiac output seems to begin at iv infusion rates as low as 1.0 micrograms/kg/minute, increases in systolic blood pressure at 2.5 micrograms/kg/minute, and heart rate changes at 5.5 micrograms/kg/minute.
The increase of dobutamine infusion rates from 10 to 20 micrograms/kg/minute Usually results in further increases in cardiac output.

Dobutamine stress echocardiography
Ischaemic diagnostic: Due to the positive inotropic testing and in particular due to the Positive chronotropic effects under dobutamine stress, the myocardial oxygen (and substrate) demand increases. With a pre-existing coronary artery stenosis, an insufficient increase of coronary blood flow leads to local hypoperfusion, which can be demonstrated on the echocardiogram in the form of a newly developed myocardial wall motility disorder in the respective segment.
Viability diagnostic: Viable myocardium, which is hypokinetic or akinetic (due to stunning, hibernation) on the echocardiogram, has a contractile functional reserve. This contractile functional reserve is particularly stimulated by the positive inotropic effects during dobutamine stress testing at lower doses (5-20 μg/kg/min). An improvement of the systolic contractility, i.e. increase of wall motility in the respective segment, can be shown on the echocardiogram.

5.2 Pharmacokinetic properties:

Onset of action is 1 - 2 minutes after the start of infusion; during continuing infusion, steady-state plasma levels are only reached after 10 - 12 minutes. Steady-state plasma levels increase dose-dependently linearly to the infusion rate. Halflife is 2 - 3 minutes, distribution volume is 0.2 l/kg, plasma clearance is not dependent on cardiac output and is 2.4l/min/m2. Dobutamine is mainly metabolised in the tissue and liver. It is mainly metabolised to conjugated glucuronides as well as the pharmacologically inactive 3-Omethyldobutamine. The metabolites are mainly excreted in urine (more than 2/3 of the dose), and to a lesser extent in bile.

Paediatric population

In most paediatric patients, there is a log-linear relationship between plasma Dobutamine concentration and hemodynamic response that is consistent with a threshold model. Dobutamine clearance is consistent with first-order kinetics over the dosage range of 0.5 to 20 micrograms/kg/minute. Plasma dobutamine concentration can vary as much as two-fold between paediatric patients at the same infusion rate and

there is a wide variability in both the plasma dobutamine concentration necessary to initiate a hemodynamic response and the rate of hemodynamic response to increasing plasma concentrations. Therefore, in clinical situations dobutamine infusion rates must be individually titrated.

5.3 Pre-clinical Safety Data:

Preclinical data reveal no special hazard for humans based on conventional studies Of safety pharmacology and repeated dose toxicity. There are no studies concerning the mutagenic and carcinogenic potential of dobutamine. In view of the vital indications and the short duration of treatment these studies appear of minor relevance. Studies in rats and rabbits revealed no evidence of a teratogenic effect. An impairment of implantation and pre- and postnatal growth retardations were observed in rats at doses toxic to mothers.

No influence on fertility was seen in rats.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

1. Disodium Edetate USP
2. Polyethylene Glycol 400 USP
3. DBH-Solu. In-house
4. Ascorbic Acid USP
5. Sodium Metabisulphite USP
6. Activated Charcoal USP
7. Water for Injection USP

6.2 Incompatibilities:

Because of potentialphysical 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 bisulfate and ethanol.

6.3 Shelf – life:

24 Months

6.4 Special precautions for storage:

Store below 30°C., protected from light. Do not freeze

6.5 Nature and contents of container:

5 ampoules of 5ml packed in a unit carton, 5 such unit cartons are packed in parcel pack and 16 such parcel packs are packed in a shipper pack.

6.6 Special Precautions for Handling and Disposal:

In case of dilution the solution for infusion should be diluted immediately before use. For dilution, a compatible infusion solution should be used. Chemical and physical compatibility have been demonstrated with 5% glucose solution, 0.9% sodium chloride solution and 0.45% sodium chloride in 5% glucose solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Note:

Solutions containing Dobutamine may have a pink colouration, which may become darker over time. This is due to a slight oxidation of the active substance.

If storage instructions are observed (see also section 6.4 for Special storage instructions), there will not be a considerable loss in activity.
Immediately after opening the ampoule, there may be a sulfuric odour lasting for a short period. The quality of the medicinal product however is not impaired.

7. MARKETING AUTHORIZATION HOLDER:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. MARKETING AUTHORIZATION NUMBER:

Neon/IND/229

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION:

24/07/2019

10. DATE OF REVISION OF THE TEXT: -- July 2023

11. REFERENCE

- Dobutamine 5 mg/ml, solution for infusion - Summary of Product Characteristics (SmPC) - print friendly - (emc) (medicines.org.uk)