SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MEKARD 250 mg/20 ml concentrated solution for i.v. infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

It contains, 14 mg of dobutamine hydrochloride equivalent to 12.5 mg of dobutamine per ml, 280 mg of dobutamine hydrochloride equivalent to 250 mg of dobutamine per 20 ml ampoule.

Excipients:

Sodium metabisulfite 4.8 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for infusion.

Ampoules containing clear, colorless or light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

MEKARD is indicated when inotropic supportive therapy is required in case of low heart flow associated with heart attack, cardiomyopathy, open heart surgery, septic shock, or cardiogenic shock.
MEKARD can also be used to maintain or increase cardiac output in possitive pressure ventilation as a result of expiration.

Dobutamine stress echocardiography
MEKARD can also be used as an alternative in cardiac stress tests, in patients who cannot fully perform routine exercise. For this purpose, dobutamine should be used in units that normally perform exercise stress testing and necessary measures should be taken for the tests.

Pediatric population
Dobutamine is indicated in all pediatric age groups (from newborn to 18 years of age) in the case of low cardiac output hypoperfusion resulting from cardiac surgery, cardiogenic shock, cardiomyopathies, and heart decompensation after septic shock.

4.2 Posology and method of administration

Posology/frequency and duration of administration

Adults

The normal dose is 2.5-10 micrograms/kg/min. Occasionally, doses as low as 0.5 microgram/kg/min may produce a response. Rarely, a dose of up to 40 microgram/kg/min may be required. The rate of administration and duration of treatment should be adjusted according to the response of the patient determined by heart rate, blood pressure, urine output and, if possible, measurement of cardiac output. When MEKARD is administered at rates lower than 10 microgram/kg/min, dose-related side effects are not common. Even at high speeds as much as 40 microgram/kg/min, occasionally it is used without significant side effects. The final volume applied should be determined by the fluid requirements of the patient. In patients with limited fluid intake, high doses of up to 5,000 micrograms/ml were used. High concentrations of MEKARD should be given with an infusion pump to ensure full dosing.

Cardiac stress testing: When used as an alternative to exercise for cardiac stress testing, the recommended dose is from 5 microgram/kg/min to 20 micrograms/kg/min., additional increments of 5 microgram/kg /min. Each dose is infused for 8 minutes. Continuous ECG monitoring is required and infusion should be terminated in the case of > 3 mm ST segment depression or any ventricular arrhythmia. Furthermore, the infusion should be terminated when the heart rate reaches the maximum of age/gender, when the systolic blood pressure rises above 220 mm HG or when any side effects occur.

Pediatric population

In all pediatric patient populations (from newborn to 18 years old), the initial dose is 5 mcg/kg/min and doses between 2-20 mcg/kg/min are adjusted according to the clinical response. Sometimes doses as low as 0.5 - 1 mcg/kg/min may produce a clinical response.

There is good reason to assume that the minimum effective dose for children is higher than for adults. Care should be taken when applying high doses because there are also reasons to assume that the maximum tolerated dosage for children is lower than for adults. Most adverse reactions (especially tachycardia) are observed when the dosage is equal to or higher than 7.5 mcg/kg/min, but it is sufficient to reduce or terminate the dobutamine infusion rate to quickly reverse undesired effects.

The plasma concentration (threshold value) required to initiate the hemodynamic response in pediatric patients and the hemodynamic response rate to increased plasma concentrations have shown that the dose required for children cannot be predetermined and the dose must be titrated to provide a smaller "therapeutic window".

Application way:

For continuous infusion with infusion pump, it should be diluted with 5% Dextrose and 0.9% Sodium chloride to a concentration of 0.5 - 1 mg/mL (maximum 5 mg/mL if fluid intake is restricted). Central venous catheter should be used for infusion at higher concentrations. It is incompatible with bicarbonates and other strong alkaline solutions.

Neonatal intensive care: It should be diluted to 30 mg/kg body weight and completed with 50 mL infusion solution. Provides 5 mcg/kg/min dose when intravenous infusion rate is 0.5 mL/hour.

Method of administration:

For intravenous use only.

MEKARD should be diluted in an IV container to at least 50 ml before administration with one of the following intravenous solutions:

Sodium Chloride Intravenous solution, 5% Dextrose Intravenous solution, 5% Dextrose + 0.9% Sodium Chloride Intravenous solution, Sodium Lactate Intravenous solution.

For example, diluting to 250 or 500 ml will provide the following concentrations for administration:

250 ml contains 1,000 micrograms/ml of dobutamine.

500 ml contains 500 micrograms / ml dobutamine.

The prepared solutions should be used within 24 hours.

Because of its short half-life, MEKARD should be administered as a continuous intravenous infusion. After dilution, it should be administered via an intravenous needle or catheter by using an air reservoir or other suitable measuring device to control the flow rate.

Additional information on special populations:

Renal/Hepatic failure:

The effect of dobutamine on impaired renal and hepatic function is unknown, close monitoring is recommended.

Pediatric population:

The safety and efficacy of dobutamine in pediatric patients has not been established.

Geriatric population:

The same practices used for adults are valid.

4.3 Contraindications

It is contraindicated in individuals with hypersensitivity to Dobutamine, sodium metabisulfite or any of its ingredients.

It should not be used in patients with phaeochromocytoma.

Dobutamine Stress Cardiography

Dobutamine should not be used to detect myocardial ischemia and live myocardium in the following cases:

- Recently formed (within the last 30 days) myocardial infarction
- Unstable angina pectoris
- Left main coronary artery stenosis
- Hemodynamically significant left ventricular outflow tract obstruction including hypertrophic obstructive cardiomyopathy

- Hemodynamically significant heart valve defect
- Severe heart failure (NYHA III or IV)
- If there exist a clinically significant arrhythmia or chronic arrhythmia or especially a recurrent persistent ventricular tachycardia in patient's medical history, or if there is a predisposition to any of these conditions
- Significant disturbances in conduction
- Acute pericarditis, myocarditis or endocarditis
- Aortic dissection
- Aortic aneurysm
- Poor ultrasound imaging conditions
- Inadequate treatment / controlled arterial hypertension
- Venticular filling obstruction (constructive pericarditis, pericardial tamponade)
- Hypovolaemia
- Hypersensitivity to dobutamine in patient's history

4.4 Special warnings and precautions for use

Adults

If an increase in heart rate or systolic blood pressure occurs or if arrhythmia is accelerated, the dose of dobutamine should be reduced or the drug administration should be terminated temporarily. Dobutamine may accelerate or exacerbate ventricular ectopic activity, which rarely causes ventricular tachycardia or fibrillation. Because Dobutamine facilitates A-V delivery, patients with atrial flutter or fibrillation may give rapid ventricular responses.

When dobutamine is administered to patients with acute myocardial infarction, special attention is required, since any significant increase in heart rate or excessive increases in arterial pressure can exacerbate ischemia and cause anginal pain and ST segment elevation. Inotropic agents including dobutamine, do not correct hemodynamics in patients with mechanical obstruction affecting either ventricular filling or outlet, or both. Inotropic response may be insufficient in patients with significantly reduced ventricular compliance. Such conditions are present in cases of cardiac tamponade, valvular aortic stenosis and idiopathic hypertrophic subaortic stenosis.

Minimal vasoconstriction has occasionally been observed, notably in patients who have recently been treated with a β-blocker drug. The inotropic effect of dobutamine ingenerates due to stimulation of cardiac β1 receptors and is inhibited by β-blocker drugs. But dobutamine has been shown to destroy the cardiodepressive effect of β-blocker drugs. On the other hand, α blockage may develop the effects of β1 and β2, resulting in tachycardia and vasodilatation.

Dobutamine stress echocardiography

Due to the possibility of life-threatening complications, dobutamine administration for stress echocardiography should only be performed by a physician with sufficient experience in the administration of dobutamine for this indication.

The use of MEKARD as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, branch block, valvular heart disease, aortic outlet obstruction, or any cardiac condition that may make the exercise stress test inappropriate.

Cardiac rupture is a possible complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) may be affected by various factors including time and location of the infarct. Very rarely there are reports of fatal acute cardiac rupture during the dobutamine stress test. These events occurred during the pre-discharge examination in patients hospitalized with recent myocardial infarction (within 4-12 days). In reported cases of free wall ruptur, resting echocardiograms showed diskinetic and thinning inferior wall. Patients who are considered to have a risk of cardiac rupture during a Dobutamine test should therefore be carefully evaluated before testing.

Dobutamine stress echocardiography should be terminated if the following symptoms occur:

- Age - estimated maximal heart rate limit is reached [(220 - age) x 0.85]
- If systolic blood pressure is decreased more than 20 mmHg
- If blood pressure rises above 220/120 mmHg
- Increasing symptoms (angina pectoris, dyspnea, dizziness, ataxia)
- Increased arrhythmia (eg. coupling, ventricular salvo)
- Increased conduction disturbances
- New developing wall motion disorders in multiple wall segments (16-segment model)
- Increase in endsystolic volume
- Repolarization abnormality development (in patients with ischemia-induced, non-myocardial infarction onset, cumulative or monophasic ST-segment elevation above 0.1 mV, more than 0.2 mV ST segment depression with horizontal or downward inclination of at 80 (60) ms)
- If the highest dose has been reached.

If serious complications occur, dobutamine stress cardography should be terminated immediately (see Section 4.8 - Undesirable Effects).

During the administration of Dobutamine concentrate, as with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure, and infusion rate should be closely monitored. When treatment is initiated, electrocardiographic monitoring is recommended until a stable response is reached.

Occasionally, rapid falls in blood pressure associated with dobutamine treatment have been identified. Dose reduction or discontinuation of infusion therapy usually results in rapid return of blood pressure to the baseline values, but rarely intervention may be required and return may not be rapid.

Dobutamine concentrate should be used with caution in the presence of severe hypertension (mean arterial pressure less than 70 mm Hg) complicated by cardiogenic shock.

When necessary, correct the hypovolemia with whole blood or plasma before administration dobutamine.

Despite adequate ventricular filling pressure and cardiac output if arterial blood pressure remains low or progressively decreases during dobutamine administration, simultaneous use of a peripheral vasoconstrictor agent such as dopamine or noradrenaline should be considered.

Pediatric Population:

Dobutamine can be administered to children with low-flow hypoperfusion resulting from decompensated heart failure, cardiac operation, cardiogenic and septic shock. The hemodynamic effect of dobutamine hydrochloride in children may be quantitatively and qualitatively different compared to adults. The gradual increase in heart rate and blood pressure can be observed more frequently and intensively in children. Pulmonary occlusion pressure in children may not fall as in adults, or may increase in newborns especially under one year of age. In the newborn, the cardiovascular system is less interoceptive to dobutamine and the incidence of hypotensive effects may be higher in adults than in young children.

Therefore, these pharmacodynamic properties should be taken into consideration and children using dobutamine should be closely monitored.

This product contains sodium metabisulphite. Rarely it may cause severe hypersensitivity reactions (severe allergy) and bronchospasm (difficulties in breathing).

This medicinal product contains less than 1 mmol (23 mg) of sodium per dose; in fact, “it does not contain sodium”.

4.5 Interaction with other medicinal products and other forms of interaction

Halogenated anesthetics:

Although the posiblity of causing ventricular arrhythmias is lower than that of adrenaline, MEKARD is used with great caution during anesthesia with cyclopropane, halothane and other halogenated anesthetics.

Entacapone:

The effects of MEKARD may vary with entacapone.

Beta Blockers:

The inotropic effect of dobutamine arises from the stimulation of cardiac β1 receptors, which can be reversed by simultaneous administration of β-blockers. Dobutamine has been shown to relieve the action of β-blocker drugs. At therapeutic doses, dobutamine has mild α1- and β2 - agonist attributes. Simultaneous administration of a non-selective β blocker such as propranolol may result in increased blood pressure due to α mediated vasoconstriction and reflex bradycardia. Like carvedilol, β-blockers with α-blocker effects may also cause hypotension during concomitant use with dobutamine due to vasodilatation caused by β2 predominance (see Section 4.4 - Special warnings and precautions for use).

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: B

Women with childbearing potential/Contraception

There is no data related MEKARD on the use in women with child-bearing potential and effects on contraception. No studies have been conducted to determine whether any contraceptive method should be used when using MEKARD.

Pregnancy

For MEKARD, data on exposure during pregnancies are not available.

Animal studies do not show any direct or harmful effects of dobutamine in relation to pregnancy / embryonal / fetal development / birth or postnatal development.

The safety for use in pregnant women has not been proven. The effect of dobutamine on the human fetus is unknown. For this reason, MEKARD should only be used in cases where the clinical advantages to be provided are higher than the possible risks to the fetus.

Lactation

It is not known whether dobutamine is excreted in human milk. The excretion of dobutamine with milk has not been investigated in animals. When deciding whether to stop breastfeeding or whether to stop/avoid treatment, the benefit of breastfeeding for the child and the benefit of the MEKARD treatment for a breastfeeding mother should be taken into account.

Fertility

Reproduction studies in rats and rabbits did not reveal any evidence that due to dobutamine, fertility was impaired, damage to fetus or teratogenic effect.

4.7 Effects on ability to drive and use machines

This section does not apply due to indications of use and very short half-life.

4.8 Undesirable effects

In infusions up to 72 hours, any adverse effects other than adverse effects seen with short-term infusions did not appeared. There is evidence of partial tolerance to 72 hours or more continuous MEKARD infusion, so that higher doses may be required to achieve the same effects.

These are classified as very common (≥1 / 10), common (≥1 / 100 to <1/10), uncommon (≥1 / 1,000 to <1/100) and rare (≥1 / 10,000 to <1 / 1,000), very rare (<1 / 10,000) and unknown (cannot be estimated from the available data).

Immune system diseases

Unknown: Hypersensitivity reactions including urticaria, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and serious life-threatening asthma episodes may occur due to sulphite sensibility (see Section 4.4 - Special warnings and precautions for use).

Blood and lymphatic system diseases

Common: Eosinophilia, inhibition of blood platelet aggregation (only in ongoing infusions for days).

Metabolism and nutritional diseases

Very rare: hypokalemia

Pychiatric diseases

Unknown: Feeling of restlessness, heat and anxiety

Diseases of the nervous system

Common: Headache

Unknown: Paresthesia, tremor, myoclonic spasm. Myoclonus has been reported in patients with severe renal failure and who take dobutamine.

Cardiac diseases

Very common: Increased (≥ 30 beat / minute) heart rate

Common: Ventricular dysrhythmia, dose-dependent ventricular extrasystoles, palpitations. Increased ventricular frequency in patients with atrial fibrillation. These patients should be observed before dobutamine infusion.

Uncommon: Ventricular tachycardia, ventricular fibrillation.

Very rare: Bradycardia, myocardial ischemia, myocardial infarction, cardiac arrest.

Unknown: Eosinophilic myocarditis was found at the explant hearts in patients receiving multiple treatment with dobutamine or other inotropic agents before transplantation.

ST segment increase in electrocardiogram.

In children: A marked reduction in heart rate and / or blood pressure, as well as a lower reduction in pulmonary capillary pressure compared to adults.

Vascular diseases

Common: ≥50 mmHg blood pressure increase, angina pain. In particular, vasoconstriction in patients previously treated with beta receptor blockers.

Unknown: Decrease in pulmonary capillary pressure.

Gastrointestinal diseases

Unknown: Nausea.

Kidney and urinary disorders

Unknown: urine jam

Dobutamine stress echocardiography

Cardiac diseases

Very common: Ventricular extra-systolicysis at a frequency of > 6/min. Common: Supraventricular extrasystole, ventricular tachycardia

Uncommon: Ventricular fibrillation, myocardial infarction Very rare: Secondary atrioventricular block formation, palpitations Unknown: Stress cardiomyopathy, fatal heart rupture

Vascular diseases

Very common: Pectoral angina disorder

Very rare: coronary vasospasm, hypertensive / hypotensive blood pressure decompensation, intracavitary pressure gradient formation

Unknown: Left ventricular outflow tract obstruction

Respiratory, chest disorders and mediastinal diseases

Common: Bronchospasm, difficulty in breathing (apnoea / dyspnoea)

Gastrointestinal diseases

Common: Nausea

Skin and subcutaneous tissue diseases

Common: Exanthema

Very rare: Petesial bleeding

Musculoskeletal disorders, connective tissue and bone diseases

Common: Chest pain

Kidney and urinary tract diseases

Common: Increasing urinary urgency in high-dose infusion

Unknown: Urinary urgency

General disorders and diseases related to the application area

Common: Fever, phlebitis at the injection site. Local inflammation may develop in case of accidental paravenous leakage.

Very rare: Skin necrosis

Pediatric population

Side effects, including systolic blood pressure elevation, systemic hypertension or hypotension, tachycardia, headache, pulmonary congestion, and pulmonary occlusion pressure elevation which causes edema, and symptomatic complaints may be observed.

<u>Reporting of suspected adverse reactions</u>

Reporting any suspected adverse reactions of drugs is very important. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0312 218 35 99).

4.9 Overdose and therapy

Overdose has been reported rarely. Symptoms of toxicity include anorexia, nausea, vomiting, tremor, anxiety, palpitation, headache, difficulty in breathing, anginal and nonspecific chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachyarrhythmia, myocardial ischemia and ventricular fibrillation. Hypotension may occur due to vasodilatation.

The duration of action of dobutamine hydrochloride is generally short (half-life about 2 minutes). Dobutamine infusion should be temporarily discontinued until the patient's condition stabilizes. The patient should be monitored and appropriate resuscitative measurements should be initiated immediately. Difficult diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion were not determined as useful. If swallowed, unexpected absorption may occur through the mouth and gastrointestinal tract.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Adrenergic and Dopaminergic drugs

ATC Code: C01CA07

Dobutamine stimulates direct β-adrenergic receptors and is generally thought to be a selective β1-adrenergic agonist. The mechanism of action of the drug is complicated. The β-adrenergic effects are thought to be due to stimulation of adenylate cyclase activity. At therapeutic doses, dobutamine has mild β2 and α1 adrenergic receptor agonist effects, which are relatively stable and result in minimal net direct effect on systematic vasculature. Unlike dopamine, dobutamine does not cause endogenous norepinephrine release. The main effect of therapeutic doses of dobutamine is cardiac stimulation.

While the positive inotropic effect of the drug on myocardium is mainly indicated by β1-adrenergic stimulation, the experimental findings suggest that α1-adrenergic stimulation may be involved, and that α1-adrenergic activity is mainly due to the (-) - stereoisomer of the drug.

The β1-adrenergic effects of dobutamine have a positive inotropic effect on the myocardium and result in increased myocardial contractility and due to heart rate volume an increase in cardiac output in healthy individuals and in patients with congestive heart failure. At therapeutic doses, dobutamine causes a reduction in peripheral resistance, but systolic blood pressure and pulse pressure may remain unchanged or may be increased due to increased cardiac output. With normal doses, heart rate usually does not change significantly. Coronary blood flow and myocardial oxygen consumption generally increase due to increased myocardial contractility.

Electrophysiological studies have shown that dobutamine facilitates atrio-ventricular conduction and shortens intraventricular conduction or does not cause significant change. Dobutamine tendency in inducing cardiac arrhythmias may be less than dopamine and is considerably lower

than isoproterenol or other catecholamines. If it is initially elevated, pulmonary vascular resistance may decrease and mean pulmonary artery pressure may decrease or remain unchanged. Unlike dopamine, dobutamine does not affect dopaminergic receptors and does not cause renal or mesenteric vasodilatation, but urine output may be increased due to increased cardiac output.

5.2 Pharmacokinetic properties

General properties:

Absorption:

Following the I.V. administration, the onset of its effect is within 2 minutes. Peak plasma concentrations and maximum effects are reached within 10 minutes. The effect of the drug ends shortly after the termination of the infusion.

Distribution:

The volume of distribution is about 20% of the body weight. It is not known whether it has permeate to breast milk and placenta.

Biotransformation

The liver and other tissues are also metabolised by catechol-0-methyl transferase to its inactive compounds (3-0-methyl dobutamine and dobutamine conjugates). These compounds are conjugated with glucuronic acid.

Elimination:

The plasma half-life of Dobutamine is 2 minutes. The clearance rate in human blood is 2.4 L/min/m². Most of the 3-0-methyl dobutamine and dobutamine conjugates are excreted in the urine and very few are removed by feces.

Linearity/Non-linearity:

There is a linear correlation between blood levels and infusion rates.

Pediatric population

In most pediatric patients, there is a log-linear relationship between plasma dobutamine concentration and hemodynamic response consistent with the threshold pattern.

Dobutamine clearance is consistent with first order kinetics in the dose range of 0.5 to 20 micrograms/kg/min.

Plasma dobutamine concentration can vary twice as much among pediatric patients at the same infusion rate, and there is a wide variation in both the plasma dobutamine concentration required to initiate the hemodynamic response and the ratio of hemodynamic response to increased plasma concentration.

5.3 Preclinical safety data

No additional information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium metabisulphite

Water for injection

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Do not mix MEKARD with 5% sodium bicarbonate intravenous infusion or other strong alkaline solutions. Due to possible physical incompatibilities it is not recommended to mix dobutamine hydrochloride with other drugs in the same solution. MEKARD should not be used with diluents or other agents that contain both sodium metabisulfite and ethanol.

6.3 Shelf Life

24 Month

6.4 Special precautions for storage

Store at room temperature below 25 °C, in its own cardboard box.

Furthermore, It is stable for 24 hours at room temperature below 25 °C when diluted with 0.9% NaCl, 5% dextrose, 0.9% NaCl + 5% dextrose and sodium lactate solutions.

6.5 Nature and contents of container

10 pieces of colorless type I glass ampoule containing 20 ml of solution in cardboard box.

6.6 Special precautions for disposal and other handling

Disposable. Discard unused contents.

Any unused product content or waste material must be disposed of in accordance with local requirements.

Do not use if there is any color change.

Unused product contents or waste materials must be disposed of in accordance with the “Medical Waste Control Regulation” and “Packaging and Packaging Waste Control Regulations”.

7. MARKETING AUTHORISATION HOLDER

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