# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. Name of the medicinal product
Dobutamine hydrochloride 250 mg per 20 mL concentrate for solution for infusion
Mekard

## 2. Qualitative and quantitative composition
Each mL of solution contains 12.5 mg of dobutamine hydrochloride.

Excipient with known effect
Each mL of solution **also** contains 0.24 mg of sodium metabisulphite (see section 4.4).

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form
Concentrate for solution for infusion.

A clear, colourless or light-yellow solution.

## 4. Clinical particulars

### 4.1 Therapeutic indications
Sterile dobutamine hydrochloride solution is indicated in adults who require inotropic support in the treatment of low-output cardiac failure associated with cardiomyopathies, cardiogenic or septic shock, myocardial infarction and cardiac surgery. Dobutamine can increase or maintain cardiac output during positive end-expiratory pressure (PEEP) ventilation.

Dobutamine hydrochloride may also be used for cardiac stress testing as an alternative to exercise in patients for whom routine exercise cannot be satisfactorily performed. This use of dobutamine should only be undertaken in units, which already perform exercise stress testing and all normal care and precautions required for such testing are also required when using dobutamine for this purpose.

### 4.2 Posology and method of administration
This is a potent drug. The solution must be diluted to at least 50ml before administration and may then be administered by intravenous infusion.

Alkaline solutions such as 5% sodium bicarbonate should not be added to dobutamine hydrochloride because the drug will be inactivated.

Sterile dobutamine hydrochloride solution must be diluted to at least 50ml with one of the following intravenous solutions:
1. Sodium chloride intravenous infusion BP 0.9% w/v
2. Dextrose intravenous infusion BP 5% w/v
3. 5% dextrose and 0.9% sodium chloride intravenous infusion BP
4. 5% dextrose and 0.45% sodium chloride intravenous infusion
5. Sodium lactate intravenous infusion BP.

If not required immediately, the diluted solution may be stored for up to 24 hours in a refrigerator. Dobutamine should be administered as a continuous infusion because of its short half-life.

A suitable metering device is required in the infusion system to control the rate of flow and this should be adjusted to the optimum patient response and monitored constantly in the light of the individual patient's response.

Recommended dosage for adults and the elderly:
The usual dose is 2.5 to 10 micrograms/kg/minute. Occasionally, however, a dose as low as 0.5 micrograms/kg/minute will elicit a response. Up to 40 micrograms/kg/minute may occasionally be required.

The rate of administration and duration of therapy should be adjusted according to the patient's response as determined by heart rate, blood pressure, urine flow and, if possible, measurement of cardiac output.

It is advisable to reduce the dosage of dobutamine hydrochloride gradually rather than abruptly stopping therapy.

Side effects which are dose-related, are infrequent when dobutamine hydrochloride is administered at rates below 10 micrograms/kg/minute. Rates as high as 40 micrograms/kg/minute have been used occasionally without significant adverse effects.

The final volume administered should be determined by the fluid requirements of the patient. Concentrations as high as 5,000 micrograms/ml have been used in patients with restricted fluid intake. High concentrations of dobutamine should be given with an infusion pump, to ensure accurate dosage.

Cardiac stress testing: when used as an alternative to exercise for cardiac stress testing the recommended dose is an incremental increase of 5 micrograms/kg/minute from 5 up to 20 micrograms/kg/minute, each dose being infused for 8 minutes. Continuous ECG monitoring is essential, and the infusion is terminated in the event of >3mm ST segment depression or any ventricular arrhythmia. The infusion should also be terminated if the heart rate reaches the age/sex maximum, systolic blood pressure rises above 220mm HG or any side effects occur.

Children:
The safety and efficacy of dobutamine hydrochloride therapy in children have not been established.

**Method of administration**
Intravenous infusion.

**4.3 Contraindications**

- Hypersensitivity to dobutamine, sodium metabisulphite or any of the excipients listed in section 6.1.
- Phaeochromocytoma.
- Dobutamine stress echocardiography.
- Dobutamine must not be used for the detection of myocardial ischaemia and of viable myocardium in case of:

- recent myocardial infarction (within the last 30 days)
- unstable angina pectoris
- stenosis of the main left coronary artery
- haemodynamically significant outflow obstruction of the left ventricle including hypertrophic obstructive cardiomyopathy
- haemodynamically significant cardiac valvular defect
- severe heart failure (NYHA III or IV)
- predisposition for or documented medical history of clinically significant or chronic arrhythmia, particularly recurrent persistent ventricular tachycardia
- significant disturbance in the conduction
- acute pericarditis, myocarditis or endocarditis
- aortic dissection
- aortic aneurysm
- poor sonographic imaging conditions
- inadequately treated/controlled arterial hypertension
- obstruction of ventricular filling (constrictive pericarditis, pericardial tamponade)
- hypovolaemia

**4.4 Special warnings and precautions for use**

The dose of dobutamine should be reduced or the drug should be discontinued temporarily if an undue increase in heart rate or systolic blood pressure occurs or if an arrhythmia is precipitated. Dobutamine may precipitate or exacerbate ventricular ectopic activity: rarely has it caused ventricular tachycardia or fibrillation. Because dobutamine facilitates A-V conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

Dobutamine should only be used with great care in patients with acute myocardial infarction because any significant increase in heart rate or excessive increase in arterial pressure that occurs may intensify ischaemia and cause anginal pain and ST-segment elevation.

Inotropic agents, including dobutamine, do not improve haemodynamics in most patients with mechanical obstruction that hinders either ventricular filling 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. The inotropic effect of dobutamine stems from stimulation of cardiac β1 receptors and this effect is prevented by β-blocking drugs. However, dobutamine has been shown to counteract the cardio-depressive effects of β-blocking drugs. Conversely, adrenergic blockade may make the β1 and β2 effects apparent, resulting in tachycardia and vasodilatation.

***Dobutamine stress echocardiography***

Because of possible life-threatening complications, the administration of dobutamine for stress echocardiography should only be undertaken by a physician with sufficient personal experience of the use of dobutamine for this indication.

The use of dobutamine as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, bundle branch block, valvular heart disease,

aortic outflow obstruction or any cardiac condition that could make them unsuitable for exercise stress testing.

Cardiac rupture is a potential complication of myocardial infarction. The risk of cardiac rupture (septal and free wall) may be influenced by a variety of factors including the site, and time since, the infarct. There have been very rare, fatal reports of acute cardiac rupture during dobutamine stress testing. These events have occurred during pre-discharge examination in patients hospitalised with recent (within 4-12 days) myocardial infarction. In the reported cases of free wall rupture, the resting echocardiogram showed a dyskinetic and thinned inferior wall. Patients considered at risk of cardiac rupture during dobutamine testing should therefore be carefully evaluated prior to testing.

Dobutamine stress echocardiography must be discontinued if one of the following diagnostic endpoints occurs:

- reaching the age-predicted maximal heart rate [(220-age in years) x 0.85]
- systolic blood pressure decrease greater than 20 mmHg
- blood pressure increase above 220/120 mmHg
- progressive symptoms (angina pectoris, dyspnoea, dizziness, ataxia)
- progressive arrhythmia (e.g., coupling, ventricular salvos)
- progressive conduction disturbances
- recently developed wall motility disorders in more than 1 wall segment (16-segment model)
- increase of end-systolic volume
- development of repolarisation abnormality (due to ischaemia horizontal or downsloping ST segment depression more than 0.2 mV at an interval of 80 (60) ms after the J point compared to baseline, progressive or monophasic ST-segment elevation above 0.1 mV in patients without a previous myocardial infarction
- reaching peak dose

In the event of serious complications (see section 4.8) dobutamine stress echocardiography must be stopped immediately.

During the administration of dobutamine, as with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure, and infusion rate should be monitored closely. When initiating therapy, electrocardiographic monitoring is advisable until a stable response is achieved.

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, but rarely intervention may be required and reversibility may not be immediate.

Dobutamine should be used with caution in the presence of severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70mm HG).

If hypovolaemia is present, it should be corrected by administration of either whole blood or plasma before using dobutamine hydrochloride.

If arterial blood pressure remains low or decreases progressively during the administration of dobutamine despite adequate ventricular filling pressure and cardiac output, consideration may

be given to the concomitant use of a peripheral vasoconstrictor agent, such as dopamine or noradrenaline.

Stress cardiomyopathy (Takotsubo syndrome) is a possible severe complication of the use of dobutamine during stress echocardiography (see section 4.8). The administration of dobutamine for stress echocardiography should be only undertaken by a physician experienced with the procedure. The physician should be vigilant during the test and the recovery period and be prepared for appropriate therapeutic intervention during the test. In the event of stress cardiomyopathy (Takotsubo syndrome) dobutamine should be stopped immediately.

*Excipients*
This medicine contains **sodium metabisulphite**, which may rarely cause severe hypersensitivity reactions and bronchospasm.

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

*Halogenated anaesthetics:*
Although it is less likely than adrenaline to cause ventricular arrhythmias, Dobutamine solution should be used with great caution during anaesthesia with cyclopropane, halothane and other halogenated anaesthetics.

*Entacapone*:
The effects of dobutamine 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 (see section 4.4 Special warnings and precautions for use).

**4.6 Pregnancy and lactation**
Animal studies have not revealed any evidence of teratogenic effects from dobutamine hydrochloride. As animal reproduction studies are not always predictive of human response, the drug should not be used in pregnancy unless, in the opinion of the physician, the expected therapeutic benefits outweigh the potential risk to the foetus.

**4.7 Effects on the ability to drive and use machines**
Dobutamine hydrochloride has no/negligible influence on the ability to drive or use machines.

**4.8 Undesirable effects**
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 solution for 72 hours or more; therefore, higher doses may be required to maintain the same effects.

Evaluation of undesirable effects is based on the following frequency scale:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

*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 sulphite sensitivity (see section 4.4 Special warnings and other precautions for use).

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

*Metabolism and nutrition disorders:*
Very rare: Hypokalaemia
Consideration should be given to monitoring serum potassium.

*Cardiac 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 before dobutamine infusion.
Vasoconstriction 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 before transplantation.
Stress cardiomyopathy (Takotsubo syndrome) (see section 4.4)

*Vascular disorders:*
Hypertension. A marked increase in systolic blood pressure indicates overdose (see also section 4.5 Interactions).
Hypotension (see sections 4.4 Special warnings and precautions for use, 4.5 Interactions)

*Nervous system disorders:*
Common: Headache

Not known: Paraesthesia, tremor, myoclonic spasm. Myoclonus has been reported in patients with severe renal failure receiving dobutamine.

*Gastrointestinal disorders*
Not known: Nausea

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

*Renal and urinary disorders*
Not known: Urinary urgency

*Dobutamine stress echocardiography*

*Cardiac disorders / vascular disorders*
Very common: Pectoral anginal discomfort, ventricular extra-systoles with a frequency of > 6/min
Common: Supraventricular extrasystoles, ventricular tachycardia
Uncommon: Ventricular fibrillation, myocardial infarction
Very rare: Occurrence of a second-degree atrioventricular block, coronary vasospasms. Hypertensive/hypotensive blood pressure decompensation, occurrence of an intracavitary pressure gradient, palpitations.
Not known: Stress cardiomyopathy
Left ventricular outflow tract obstruction
Fatal cardiac rupture

*Respiratory system, thoracic and mediastinal disorders*
Common: Bronchospasm, shortness of breath

*Gastrointestinal disorders*
Common: Nausea

*Skin and subcutaneous tissue disorders*
Common: Exanthema
Very rare: Petechial bleeding

*Musculoskeletal and connective tissue disorders*
Common: Chest pain

*Renal and urinary disorders*
Common: Increased urgency at high dosages of infusion

*General disorders and administration site conditions*
Common: Fever, phlebitis at the injection site
In case of accidental paravenous infiltration, local inflammation may develop.
Very rare: Cutaneous necrosis

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

**4.9 Overdose**
Overdoses of dobutamine have been reported rarely. The symptoms of toxicity may include anorexia, nausea, vomiting, tremors, anxiety, palpitations, headache, shortness of breath and anginal and non-specific chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachyarrhythmias, myocardial ischaemia and ventricular fibrillation. Hypotension may result from vasodilatation.

Because the half-life of dobutamine is only about 2 minutes adverse effects may be corrected by discontinuing or reducing the rate of infusion as appropriate. The patient should be monitored and any appropriate resuscitative measures initiated promptly.

Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial.

If the product is ingested, unpredictable absorption may occur from the mouth and gastrointestinal tract.

## 5. Pharmacological properties

**5.1 Pharmacodynamic properties**
Pharmacological classification: 12.7 Sympathomimetic cardiac stimulants.

Dobutamine directly stimulates $\beta_1$ adrenergic receptors and is generally considered a selective $\beta_1$-adrenergic agonist, but the mechanisms of action of the drug are complex. It is believed that the β-adrenergic effects result from stimulation of adenyl cyclase activity. In therapeutic doses, dobutamine also has mild $\beta_2$ and ∝-adrenergic receptor agonist effects, which are relatively balanced and result in a minimal net direct effect on system vasculature. Unlike dopamine, dobutamine does not cause the release of endogenous norepinephrine. The main effect of therapeutic doses of dobutamine is cardiac stimulation. The positive inotropic effect of the drug on the myocardium appears to be mediated principally via $\beta_1$-adrenergic stimulation. Experimental evidence suggests that $\propto_1$ adrenergic stimulation may also be involved and that the $\propto_1$- adrenergic activity results mainly from the (-) stereoisomer of the drug.

The $\beta_1$-adrenergic effects of dobutamine exert a positive inotropic effect on the myocardium and result in an increase in cardiac output due to increased myocardial contractility and stroke volume in healthy individuals and in patients with congestive heart failure. Increased left ventricular filling pressure decreases in patients with congestive heart failure. In therapeutic doses, dobutamine causes a decrease in peripheral resistance; however systolic blood pressure and pulse pressure may remain unchanged or be increased because of augmented cardiac output. With usual doses, heart rate is usually not

substantially changed. Coronary blood flow and myocardial oxygen consumption are usually increased because of increased myocardial contractility.

Electrophysiologic studies have shown that dobutamine facilitates atrioventricular conduction and shortens or causes no important change in intraventricular conduction. The tendency of dobutamine to induce cardiac arrhythmias may be slightly less than that of dopamine and is considerably less than that of isoproterenol or other catecholamines. Pulmonary vascular resistance may decrease if it is elevated initially and mean pulmonary artery pressure may decrease or remain unchanged. Unlike dopamine, dobutamine does not seem to affect dopaminergic receptors and causes no renal or mesenteric vasodilation, however, urine flow may increase because of increased cardiac output.

### 5.2 Pharmacokinetic properties

Absorption
Orally administered dobutamine is rapidly metabolised in the gastrointestinal tract. Following IV administration, the onset of action of dobutamine occurs within 2 minutes. Peak plasma concentrations of the drug and peak effects occur within 10 minutes after initiation of an IV infusion. The effects of the drug cease shortly after discontinuing an infusion.

Distribution
It is not known if dobutamine crosses the placenta or is distributed into milk.

Elimination
The plasma half-life of dobutamine is about 2 minutes. Dobutamine is metabolised in the liver and other tissues by catechol-o-methyltransferase to an inactive compound, 3-O-methyldobutamine and by conjugation with glucuronic acid. Conjugates of dobutamine and 3-O-methyldobutamine are excreted mainly in urine and to a minor extent in faeces.

### 5.3 Preclinical 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
Sodium metabisulphite
Sodium hydroxide
Hydrochloric acid
Water injection

### 6.2 Incompatibilities
Dobutamine solutions have proven to be incompatible with:
- alkaline solutions (e.g., sodium hydrogen carbonate),
- solutions containing both sodium metabisulfite and ethanol,

- aciclovir,
- alteplase,
- aminophylline,
- bretylium,
- calcium chloride,
- calcium gluconate,
- cefamandol formiate,
- cephalothin sodium,
- cephazolin sodium,
- diazepam,
- digoxin,
- etacrynic acid (sodium salt),
- furosemide,
- heparin sodium,
- hydrogen cortisone sodium succinate,
- insulin,
- potassium chloride,
- magnesium sulfate,
- penicillin,
- phenytoin,
- streptokinase,
- verapamil.

Furthermore, known incompatibilities for sodium metabisulfite are:
- chloramphenicol,
- cisplatin.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3 Shelf life**
24 months.

**6.4 Special precautions for storage**
Store below 30°C.

After first opening/dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25° C. 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 and would normally not be longer than 24 hours at 2° C to 8° C unless preparation has taken place in controlled and validated aseptic conditions.

**6.5 Nature and contents of the container**
A clear, colourless type I glass ampoule.

Fill volume: 20 mL.
Pack size: 10 ampoules per carton.

**6.6 Special precautions for disposal and other handling**
Must be diluted to at least 50 ml with one of the intravenous solutions listed in section 4.2 before use. If not required immediately, the diluted solution may be stored for up to 24 hours in a refrigerator. If only part is used, discard the remaining solution.

## 7. APPLICANT
WMT Pharmaceuticals
Bay 559A Steven Drive, Msasa
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## 8. MANUFACTURER
Aroma Ilac Sanayi Ltd STI
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Turkey

## 9. REGISTRATION DETAILS
Zimbabwe registration number: 2023/12.7/6511
Zimbabwe category for distribution: Prescription Preparations (P.P.)

## 10. DATE OF REVISION OF THE TEXT
March 2024