Bundesinstitut
für Arzneimittel
und Medizinprodukte

HAUSANSCHRIFT Kurt-Georg-Kiesinger-Allee 3
53175 Bonn
TEL +49 (0)228 99 307-0
FAX +49 (0)228 99 307-5207
E-MAIL poststelle@bfarm.de
INTERNET www.bfarm.de

hameln pharma gmbh
Inselstraße 1
31787 Hameln
Deutschland

**Antrag vom 27.07.2022 auf Erteilung einer Gestattung gemäß §§ 10 Absatz 1a und 11 Absatz 1c Arzneimittelgesetz (AMG) – Einfuhr und Inverkehrbringen von Dobutamin-hameln 12,5 mg/ml und Dobutamin-hameln 5 mg/ml**

| Arzneimittelbezeichnung | Zulassungsinhaber | Zulassungsnummer |
|---|---|---|
| **Dobutamin-hameln 12,5 mg/ml** | **hameln pharma gmbh** | **51613.01.00** |
| **Dobutamin-hameln 5mg/ml** | **hameln pharma gmbh** | **51613.00.01** |

Sehr geehrte Damen und Herren,
auf Ihren mit E-Mail vom 27. Juli 2022 gestellten Antrag ergeht folgender

BESCHEID:

1. Es wird im Einzelfall gestattet, dass das o. g. Arzneimittel mit der für den englischen Markt bestimmten und damit mit einer in einer anderen als der deutschen Sprache verfassten Kennzeichnung und Packungsbeilage in den Verkehr gebracht wird.
2. Diese Gestattung ist befristet bis zum 30. November 2022.

Begründung:

Zu 1.
Nach §§ 10 Absatz 1a und 11 Absatz 1c AMG kann die zuständige Bundesoberbehörde im Fall eines drohenden oder bestehenden Versorgungsengpasses auf Antrag des Zulassungsinhabers im Einzelfall gestatten, dass ein Arzneimittel, das durch Ärzte unmittelbar an Patienten angewendet wird, befristet mit einer Kennzeichnung und Packungsbeilage in einer anderen als der deutschen Sprache in den Verkehr gebracht wird.
Bei der von Ihnen mit dem Antrag vorgelegten und für den englischen Markt bestimmten Kennzeichnung/Packungsbeilage handelt es sich um eine Kennzeichnung/Packungsbeilage in einer anderen als der deutschen Sprache.
Die gesetzlichen Voraussetzungen sind vorliegend erfüllt, da das in Rede stehende Arzneimittel unmittelbar durch Ärzte an Patienten abgegeben wird.

Dobutamin-hameln 12,5 mg/ml und 5 mg/ml ist indiziert, wenn eine positiv inotrope Behandlung erforderlich ist für Patienten mit kardialer Dekompensation infolge einer eingeschränkten myokardialen Kontraktilität, die entweder bedingt ist durch eine organische Herzerkrankung oder durch einen herzchirurgischen Eingriff, vor allem, wenn es sich um eine kardiale Dekompensation mit vermindertem Herzzeitvolumen (low cardiac output) und erhöhtem Pulmonalkapillar-Druck (PCP) handelt.

Im Rahmen der durch das BfArM aktuell durchgeführten Sachverhaltsermittlung wurde eine drohende versorgungsrelevante Lieferengpasssituation festgestellt. Aufgrund von aktuellen Lieferengpassmeldungen stehen wirkstoff- und darreichungsgleiche Arzneimittel aktuell nicht in den Bedarf deckendem Umfang zur Verfügung. Das Inverkehrbringen der in Rede stehenden Ware dient der Sicherstellung der Patientenversorgung.

Aus medizinischer Sicht haben verschiedene Arzneimittel zur Unterstützung der Kreislauffunktion unterschiedliche pharmakologische Charakteristika. So eignen sich weitere Substanzen der Substanzklasse nicht ausreichend und können nicht deckungsgleich zu Dobutamin eingesetzt werden.

Zu 2.
Die Befristung erfolgt antragsgemäß, stützt sich auf §§ 10 Absatz 1a und § 11 Absatz 1c AMG und ist im genannten Zeitraum ausreichend, um den drohenden Versorgungsengpass mit dem o. g. Arzneimittel auf dem deutschen Markt abzuwenden. Nach derzeitigem Informationsstand ist ab 1. Dezember 2022 wieder von einer ausreichenden Verfügbarkeit von Ware in deutscher Aufmachung auszugehen.

Hinweis:
Es wird empfohlen, aus Gründen der Nachvollziehbarkeit und Transparenz ein offizielles Informationsschreiben inklusive eines Links zur elektronischen Verfügbarkeit der Produktinformationstexte in deutscher Aufmachung jeder Lieferung beizufügen.

Rechtsbehelfsbelehrung:
Gegen diesen Bescheid kann innerhalb eines Monats nach Bekanntgabe Widerspruch erhoben werden. Der Widerspruch ist bei dem Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in Bonn einzulegen.

Bonn, den 04.08.2022

Mit freundlichen Grüßen
Im Auftrag

Dr. Michael Horn

Anlagen
- Gebrauchsinformation – in englischer Aufmachung
- Äußere Umhüllung – in englischer Aufmachung
- Etikett – in englischer Aufmachung
- Fachinformation – in englischer Aufmachung

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Dobutamine 5 mg/ml solution for infusion**
dobutamine

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. WHAT DOBUTAMINE IS AND WHAT IT IS USED FOR

Dobutamine belongs to a group of medicines called catecholamines. It helps your heart to work more effectively. It works by strengthening the pumping action of the heart, increasing the amount of blood flow in the body and by expanding your veins and arteries.

**Dobutamine is used:**
- to treat heart failure (cardiac decompensation) if the heart is not beating strongly enough (depressed contractility),
- in heart failure where there is severe low blood pressure (hypotension),
- to detect poor blood supply to the heart (cardiac stress testing).

Paediatric population
Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.

## 2. WHAT YOU NEED TO KNOW BEFORE YOU USE DOBUTAMINE

**Do not use Dobutamine if:**
- you are **allergic** (hypersensitive) to **dobutamine** or **any of the other ingredients of this medicine** (listed in section 6). An allergic reaction may include rash, itching, difficulty in breathing or swelling of the face, lips, throat or tongue. You may know this from earlier experience.
- there is **a narrowing in your heart or blood vessels that prevents the heart from filling or ejecting blood properly** (your doctor will know this).
- there is a **lack of adequate circulatory filling** (hypovolaemia).

If you have certain heart or blood vessel disorders, Dobutamine should not be used to detect poor blood supply to your heart.

**Warnings and precautions**
Talk to your doctor before using Dobutamine.
Tell your doctor if you have any of the following conditions:
- asthma and you have been told that you are allergic to sulfites,
- severe coronary heart disease,
- acute (sudden) heart failure.

Children
Increments in heart rate and blood pressure appear to be more frequent and intense in children than in adults. The new-born baby cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect (low blood pressure) seems to be more often observed in adult patients than in small children. Accordingly, the use of dobutamine in children should be monitored closely.
Caution is advised in giving high doses of dobutamine to children. Your doctor will adjust the required dose for your child carefully.

**Other medicines and Dobutamine**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important with the following medicines as they may interact with your Dobutamine:
- beta blockers (treatment of high blood pressure and irregular heart rhythms),
- alpha blockers (treatment of high blood pressure and prostate enlargement),
- vasodilators (expanding blood vessels, used to treat an angina attack or severe heart failure),
- antidiabetics (treatment of diabetes),
- ACE inhibitors (treatment of high blood pressure and heart failure),
- dopamine (used to increasing heart rate and blood pressure),
- inhaled anaesthetics.

It may still be all right for you to receive Dobutamine and your doctor will be able to decide what is suitable for you.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine. Dobutamine should not be given to pregnant women unless medically justified. It is recommended that you stop breast-feeding during your treatment with dobutamine.

**Driving and using machines**
If you have any concerns ask your doctor or pharmacist.

**Dobutamine contains sodium metabisulfite (E223)**, which may rarely cause allergic reactions (hypersensitivity) and asthma-like symptoms (bronchospasm).

**Dobutamine contains sodium**
This medicine contains 3.06 mg **sodium** per 1 ml. Each 50 ml ampoule/vial contains 153 mg sodium. This is equivalent to 7.7% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. HOW TO USE DOBUTAMINE

Dobutamine will be given to you by specifically trained health care professionals and emergency equipment will be available.

**Dosage**
The required rate of infusion depends on your response to therapy and any side effects. Your doctor will decide the dose of Dobutamine you will be given and will adjust the flow rate and duration of your infusion.

Dosage in adults:
Most patients respond to doses of 2.5-10 micrograms of dobutamine per kg body weight per minute. Doses up to 40 micrograms of dobutamine per kg body weight per minute have been given.

Dosage in children:
For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2 – 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.
The required dose for children should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**The following side effects have been reported:**

Very common (may affect more than 1 in 10 people)
- increased heart rate
- chest pain
- heartbeat disturbances

Common (may affect up to 1 in 10 people)
- blood pressure increase or decrease
- narrowing of the blood vessels (vasoconstriction)
- irregular heartbeat (palpitations)
- fast heart rate (ventricular tachycardia)
- headache
- asthma-like symptoms (bronchospasm)
- shortness of breath
- increase in white blood cells (eosinophilia)
- inhibition of blood clot formation
- increased desire to urinate (at high doses)
- feeling sick (nausea)
- rash (exanthema)
- fever
- inflammation of the vein at the injection site (phlebitis)

Uncommon (may affect up to 1 in 100 people)
- uncontrolled contractions of the ventricles of the heart (ventricular fibrillation)
- heart attack (myocardial infarction)

Very rare (may affect up to 1 in 10,000 people)
- slow heartbeat (bradycardia)
- not enough blood supplied to the heart (myocardial ischaemia)
- low potassium (hypokalaemia)
- spots on the skin (petechial bleeding)
- heart block
- narrowing of the blood vessels supplying the heart (coronary vasospasm)

- black areas of dying skin (cutaneous necrosis)

Not known (frequency cannot be estimated from the available data)
- chest pain caused by stress (stress cardiomyopathy)
- impaired cardiac function (decrease in pulmonary capillary pressure)
- problems with your heart muscle (stress cardiomyopathy also known as Takotsubo syndrome) that present with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat when dobutamine is used for stress echocardiography test

Further undesirable effects which have been observed:
- restlessness
- pins and needles (paraesthesia)
- involuntary muscle twitches (tremor)
- feeling of heat and anxiety
- muscle spasm

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

## 5. HOW TO STORE DOBUTAMINE

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date (EXP:) printed on the pack. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice the solution is not clear and free of particles or if the container is damaged.
- This medicine does not require any special temperature storage conditions.
- Keep the ampoules/vials in the outer carton in order to protect from light.
- Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. CONTENTS OF THE PACK AND OTHER INFORMATION

**What Dobutamine contains**
The active substance is dobutamine.
1 ml solution contains 5 mg dobutamine.

Each 50 ml ampoule/vial Dobutamine contains dobutamine hydrochloride equivalent to 250 mg dobutamine.

The other ingredients are sodium metabisulfite (E223), sodium chloride, hydrochloric acid and water for injections.

**What Dobutamine looks like and contents of the pack**
Dobutamine is a clear colourless or slightly yellow solution for infusion.

Dobutamine is supplied in 50 ml clear glass ampoules or vials. It is available in original packages containing 1, 5 and 10 ampoule(s) and packs containing 1, 5, 10 and 20 vial(s).

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
hameln pharma gmbh
Inselstraße 1
31787 Hameln
Germany

**Manufacturer**
Siegfried Hameln GmbH
Langes Feld 13
31789 Hameln
Germany

**Distributor**
hameln pharma ltd
Gloucester
United Kingdom

**For any information about this medicine, please contact the Distributor.**

**This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:**

| | |
|---|---|
| DE | Dobutamin-hameln 5 mg/ml Infusionslösung |
| NL | Dobutamine-hameln 5 mg/ml i.v. infusievloeistof, oplossing voor infusie |
| UK (NI) | Dobutamine 5 mg/ml solution for infusion |

**This leaflet was last revised in February 2022.**

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**The following information is intended for healthcare professionals only:**

**PREPARATION GUIDE FOR:**

**Dobutamine 5 mg/ml solution for infusion**

Please refer to the Summary of Product Characteristics for full prescribing and other information.

## 1. NATURE AND CONTENT OF CONTAINER

1 ml solution contains 5 mg dobutamine.
Dobutamine is supplied in 50 ml clear glass ampoules or vials. It is available in original packages containing 1, 5 and 10 ampoule(s) and packs containing 1, 5, 10 and 20 vial(s).

## 2. POSOLOGY AND METHOD OF ADMINISTRATION

When used for detection of myocardial ischaemia and of viable myocardium, dobutamine may only be administered by a physician with sufficient experience in conducting cardiology stress tests. Continuous monitoring of all wall areas via echocardiography, and ECG as well as control of blood pressure is necessary.

Monitoring devices as well as emergency medicines must be available (e.g. defibrillator, I.V. beta-blockers, nitrates, etc.) and staff trained in the resuscitation procedure must be present.

The required rate of infusion depends on the patient's response to therapy and the adverse reactions experienced.

The dose of dobutamine should be gradually reduced when discontinuing therapy.

Any unused solution should be discarded.

**Dosage**

Dosage in adults:
According to experience, the majority of patients respond to doses of 2.5-10 µg dobutamine/kg/min. In individual cases, doses up to 40 µg dobutamine/kg/min have been administered.

Dosage in paediatric patients:
For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2–20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

Method of administration

If a syringe pump is used dilution is not required.

Intravenous infusion of Dobutamine is also possible after dilution with compatible infusion solutions such as: 5% glucose solution (50 mg/ml), 0.9% sodium chloride (9 mg/ml) or 0.45% sodium chloride (4.5 mg/ml) in 5% glucose solution (50 mg/ml). Infusion solutions should be prepared immediately before use.
Due to its short half-life, dobutamine must be administered as a continuous intravenous infusion.

Paediatric patients: For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% (50 mg/ml) or Sodium Chloride 0.9% (9 mg/ml). Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

**Tables, showing infusion rates with different initial concentrations for various dosages:**

One ampoule (or vial) Dobutamine 5 mg/ml (250 mg/50 ml) diluted to a solution volume of 500 ml (final concentration 0.5 mg/ml)

| Dosage range | | Specifications in ml/h* (drops/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(drops/min) | 15<br>(5) | 21<br>(7) | 27<br>(9) |
| Medium<br>5 µg/kg/min | ml/h<br>(drops/min) | 30<br>(10) | 42<br>(14) | 54<br>(18) |
| High<br>10 µg/kg/min | ml/h<br>(drops/min) | 60<br>(20) | 84<br>(28) | 108<br>(36) |

* For double concentration, i.e. 500 mg dobutamine added to 500 ml, or 250 mg added to 250 ml solution volume, infusion rates must be halved.

Dosage for syringe pumps

One ampoule (or vial) Dobutamine 5 mg/ml (250 mg/50 ml) undiluted (final concentration 5 mg/ml)

| Dosage range | | Specifications in ml/h (ml/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(ml/min) | 1.5<br>(0.025) | 2.1<br>(0.035) | 2.7<br>(0.045) |
| Medium<br>5 µg/kg/min | ml/h<br>(ml/min) | 3.0<br>(0.05) | 4.2<br>(0.07) | 5.4<br>(0.09) |
| High<br>10 µg/kg/min | ml/h<br>(ml/min) | 6.0<br>(0.10) | 8.4<br>(0.14) | 10.8<br>(0.18) |

The chosen syringe pump must be suitable for the volume and rate of administration.

## 3. CONTRAINDICATIONS

Dobutamine must not be used in case of:
- known hypersensitivity to dobutamine or to any of the excipients,
- mechanical obstruction of ventricular filling and/or of outflow, such as pericardial tamponade, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, severe aortic stenosis,
- hypovolaemic conditions.

*Dobutamine stress echocardiography*

Dobutamine must not be used for 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 conduction,
- acute pericarditis, myocarditis or endocarditis,
- aortic dissection,
- aortic aneurysm,
- in case of poor sonographic imaging conditions,
- inadequately treated / controlled arterial hypertension,
- obstruction of ventricular filling (constrictive pericarditis, pericardial tamponade),
- hypovolaemia,
- previous experience of hypersensitivity to dobutamine.

## 4. INTERACTION WITH OTHER MEDICINAL PRODUCTS

Interactions of dobutamine with the following medicinal products are observed:
- beta blockers,
- alpha blockers,
- primarily venous acting vasodilators (e.g. nitrates, sodium nitroprusside),
- ACE inhibitors (e.g. captopril),
- dopamine,
- thiamine (vitamin $B_1$),
- inhaled anaesthetics,
- atropine.

Administering dobutamine to diabetic patients may cause increased insulin demand. Thus, in diabetic patients levels should be checked when starting dobutamine therapy, changing the rate of infusion and discontinuing the infusion.
If necessary the insulin dose must be adjusted as required.

## 5. INCOMPATIBILITIES

For known incompatibilities of dobutamine solutions with several substances and of sodium metabisulfite see section 6.2 of the Summary of Product Characteristics.

This medicinal product must not be mixed with other medicinal products except with those for which compatibility is proven.

## 6. STORAGE

This medicine does not require any special temperature storage conditions.
Do not freeze.
Keep the ampoules [vials] in the outer carton in order to protect from light.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Dobutamine 12.5 mg/ml concentrate for solution for infusion**

dobutamine

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. WHAT DOBUTAMINE IS AND WHAT IT IS USED FOR

Dobutamine belongs to a group of medicines called catecholamines. It helps your heart to work more effectively. It works by strengthening the pumping action of the heart, increasing the amount of blood flow in the body and by expanding your veins and arteries.

**Dobutamine is used:**
- to treat heart failure (cardiac decompensation) if the heart is not beating strongly enough (depressed contractility),
- in heart failure where there is severe low blood pressure (hypotension),
- to detect poor blood supply to the heart (cardiac stress testing).

Paediatric population

Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.

## 2. WHAT YOU NEED TO KNOW BEFORE YOU USE DOBUTAMINE

**Do not use Dobutamine if:**
- you are **allergic** (hypersensitive) to **dobutamine** or **any of the other ingredients** of this medicine (listed in section 6). An allergic reaction may include rash, itching, difficulty in breathing or swelling of the face, lips, throat or tongue. You may know this from earlier experience.
- there is **a narrowing in your heart or blood vessels that prevents the heart from filling or ejecting blood properly** (your doctor will know this).
- there is a **lack of adequate circulatory filling** (hypovolaemia).

If you have certain heart or blood vessel disorders, Dobutamine should not be used to detect poor blood supply to your heart.

**Warnings and precautions**
Talk to your doctor before using Dobutamine.
Tell your doctor if you have any of the following conditions:
- asthma and you have been told that you are allergic to sulfites,
- severe coronary heart disease,
- acute (sudden) heart failure.

Children
Increments in heart rate and blood pressure appear to be more frequent and intense in children than in adults. The new-born baby cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect (low blood pressure) seems to be more often observed in adult patients than in small children. Accordingly, the use of dobutamine in children should be monitored closely.
Caution is advised in giving high doses of dobutamine to children. Your doctor will adjust the required dose for your child carefully.

**Other medicines and Dobutamine**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important with the following medicines as they may interact with your Dobutamine:
- beta blockers (treatment of high blood pressure and irregular heart rhythms),
- alpha blockers (treatment of high blood pressure and prostate enlargement),
- vasodilators (expanding blood vessels, used to treat an angina attack or severe heart failure),
- antidiabetics (treatment of diabetes),
- ACE inhibitors (treatment of high blood pressure and heart failure),
- dopamine (used to increase heart rate and blood pressure),
- inhaled anaesthetics.

It may still be all right for you to receive Dobutamine and your doctor will be able to decide what is suitable for you.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
Dobutamine should not be given to pregnant women unless medically justified. It is recommended that you stop breast-feeding during your treatment with dobutamine.

**Driving and using machines**
If you have any concerns ask your doctor or pharmacist.

**Dobutamine contains sodium metabisulfite (E223)**, which may rarely cause allergic reactions (hypersensitivity) and asthma-like symptoms (bronchospasm).

**Dobutamine contains sodium**
This medicine contains less than 1 mmol **sodium** (23 mg) per 20 ml, that is to say essentially ‘sodium- free’.

## 3. HOW TO USE DOBUTAMINE

Dobutamine will be given to you by specifically trained health care professionals and emergency equipment will be available.

**Dosage**
The required rate of infusion depends on your response to therapy and any side effects. Your doctor will decide the dose of Dobutamine you will be given and will adjust the flow rate and duration of your infusion.

Dosage in adults:
Most patients respond to doses of 2.5-10 micrograms of dobutamine per kg body weight per minute. Doses up to 40 micrograms of dobutamine per kg body weight per minute have been given.

Dosage in children:
For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2 – 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.
The required dose for children should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**The following side effects have been reported:**

Very common (may affect more than 1 in 10 people)
- increased heart rate
- chest pain
- heartbeat disturbances

Common (may affect up to 1 in 10 people)
- blood pressure increase or decrease
- narrowing of the blood vessels (vasoconstriction)
- irregular heartbeat (palpitations)
- fast heart rate (ventricular tachycardia)
- headache
- asthma-like symptoms (bronchospasm)
- shortness of breath
- increase in white blood cells (eosinophilia)
- inhibition of blood clot formation
- increased desire to urinate (at high doses)
- feeling sick (nausea)
- rash (exanthema)
- fever
- inflammation of the vein at the injection site (phlebitis)

Uncommon (may affect up to 1 in 100 people)
- uncontrolled contractions of the ventricles of the heart (ventricular fibrillation)
- heart attack (myocardial infarction)

Very rare (may affect up to 1 in 10,000 people)
- slow heartbeat (bradycardia)
- not enough blood supplied to the heart (myocardial ischaemia)
- low potassium (hypokalaemia)
- spots on the skin (petechial bleeding)
- heart block
- narrowing of the blood vessels supplying the heart (coronary vasospasm)
- black areas of dying skin (cutaneous necrosis)

Not known (frequency cannot be estimated from the available data)
- chest pain caused by stress (stress cardiomyopathy)
- impaired cardiac function (decrease in pulmonary capillary pressure)
- problems with your heart muscle (stress cardiomyopathy also known as Takotsubo syndrome) that present with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat when dobutamine is used for stress echocardiography test

Further undesirable effects which have been observed:
- restlessness
- pins and needles (paraesthesia)
- involuntary muscle twitches (tremor)
- feeling of heat and anxiety
- muscle spasm

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse: This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

## 5. HOW TO STORE DOBUTAMINE

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice the solution is not clear and free of particles or if the container is damaged.
- This medicine does not require any special temperature storage conditions.
- Keep the ampoules in the outer carton in order to protect from light.
- Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. CONTENTS OF THE PACK AND OTHER INFORMATION

**What Dobutamine contains**
The active substance is dobutamine.
1 ml solution contains 12.5 mg dobutamine.

Each 20 ml ampoule Dobutamine contains dobutamine hydrochloride equivalent to 250 mg dobutamine.

The other ingredients are sodium metabisulfite (E223), hydrochloric acid and water for injections.

**What Dobutamine looks like and contents of the pack**
Dobutamine is a clear, colourless or slightly yellow concentrate for solution for infusion.

Dobutamine is supplied in 20 ml clear glass ampoules. It is available in original packages containing 1, 5 or 50 ampoule(s).

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
hameln pharma gmbh
Inselstraße 1
31787 Hameln
Germany

**Manufacturer**
Siegfried Hameln GmbH
Langes Feld 13
31789 Hameln
Germany

**Distributor**
hameln pharma ltd
Gloucester
United Kingdom

**For any information about this medicine, please contact the Distributor.**

**This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:**

| | |
|---|---|
| DE | Dobutamin-hameln 12,5 mg/ml Konzentrat zur Herstellung einer Infusionslösung |
| FI | Dobutamin Hameln 12.5 mg/ml infuusiokonsentraatti, liuosta varten |
| NL | Dobutamine-hameln 12,5 mg/ml steriel concentraat, concentraat voor oplossing voor infusie |
| NO | Dobutamin Hameln 12,5 mg/ml konsentrat til infusjonsvaeske |
| SE | Dobutamin Hameln 12,5 mg/ml koncentrat till infusionsvätska, lösning |
| UK (NI) | Dobutamine 12.5 mg/ml concentrate for solution for infusion |

**This leaflet was last revised in February 2022.**

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**The following information is intended for healthcare professionals only:**

**PREPARATION GUIDE FOR:**

**Dobutamine 12.5 mg/ml concentrate for solution for infusion**

Please refer to the Summary of Product Characteristics for full prescribing and other information.

## 1. NATURE AND CONTENT OF CONTAINER

1 ml solution contains 12.5 mg dobutamine.
Dobutamine is supplied in 20 ml clear glass ampoules. It is available in original packages containing 1, 5 or 50 ampoule(s).

## 2. POSOLOGY AND METHOD OF ADMINISTRATION

When used for detection of myocardial ischaemia and of viable myocardium, dobutamine may only be administered by a physician with sufficient experience in conducting cardiology stress tests. Continuous monitoring of all wall areas via echocardiography, and ECG as well as

control of blood pressure is necessary.
Monitoring devices as well as emergency medicines must be available (e.g. defibrillator, I.V. beta-blockers, nitrates, etc.) and staff trained in the resuscitation procedure must be present.

The required rate of infusion depends on the patient's response to therapy and the adverse reactions experienced.

The dose of dobutamine should be gradually reduced when discontinuing therapy.

Any unused solution should be discarded.

**Dosage**

Dosage in adults:
According to experience, the majority of patients respond to doses of 2.5-10 µg dobutamine/kg/min. In individual cases, doses up to 40 µg dobutamine/kg/min have been administered.

Dosage in paediatric patients:
For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2– 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

Method of Administration

**The infusion solution concentrate must be diluted before administration**. It must be diluted to a volume of 50 ml or more.

Intravenous infusion of Dobutamine is also possible after dilution with compatible infusion solutions such as: 5% glucose solution (50 mg/ml), 0.9% sodium chloride (9 mg/ml) or 0.45% sodium chloride (4.5 mg/ml) in 5% glucose solution (50 mg/ml). Infusion solutions should be prepared immediately before use.
Due to its short half-life, dobutamine must be administered as a continuous intravenous infusion.

Paediatric patients: For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% (50 mg/ml) or Sodium Chloride 0.9% (9 mg/ml). Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

**Tables, showing infusion rates with different initial concentrations for various dosages:**

One ampoule Dobutamine 12.5 mg/ml (250 mg/20 ml) diluted to a solution volume of 500 ml (final concentration 0.5 mg/ml)

| Dosage range | | Specifications in ml/h* (drops/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(drops/min) | 15<br>(5) | 21<br>(7) | 27<br>(9) |
| Medium<br>5 µg/kg/min | ml/h<br>(drops/min) | 30<br>(10) | 42<br>(14) | 54<br>(18) |
| High<br>10 µg/kg/min | ml/h<br>(drops/min) | 60<br>(20) | 84<br>(28) | 108<br>(36) |

* For double concentration, i.e. 500 mg dobutamine added to 500 ml, or 250 mg added to 250 ml solution volume, infusion rates must be halved.

Dosage for syringe pumps

One ampoule Dobutamine 12.5 mg/ml (250 mg/20 ml) diluted to a solution volume of 50 ml (final concentration 5 mg/ml)

| Dosage range | | Specifications in ml/h (ml/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(ml/min) | 1.5<br>(0.025) | 2.1<br>(0.035) | 2.7<br>(0.045) |
| Medium<br>5 µg/kg/min | ml/h<br>(ml/min) | 3.0<br>(0.05) | 4.2<br>(0.07) | 5.4<br>(0.09) |
| High<br>10 µg/kg/min | ml/h<br>(ml/min) | 6.0<br>(0.10) | 8.4<br>(0.14) | 10.8<br>(0.18) |

The chosen syringe pump must be suitable for the volume and rate of administration.

## 3. CONTRAINDICATIONS

Dobutamine must not be used in case of:
- known hypersensitivity to dobutamine or to any of the excipients,
- mechanical obstruction of ventricular filling and/or of outflow, such as pericardial tamponade, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, severe aortic stenosis,
- hypovolaemic conditions.

*Dobutamine stress echocardiography*

Dobutamine must not be used for 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 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,
- previous experience of hypersensitivity to dobutamine.

## 4. INTERACTION WITH OTHER MEDICINAL PRODUCTS

Interactions of dobutamine with the following medicinal products are observed:
- beta blockers,
- alpha blockers,
- primarily venous acting vasodilators (e.g. nitrates, sodium nitroprusside),
- ACE inhibitors (e.g. captopril),
- dopamine,
- thiamine (vitamin $B_1$),
- inhaled anaesthetics,
- atropine.

Administering dobutamine to diabetic patients may cause increased insulin demand. Thus, in diabetic patients levels should be checked when starting dobutamine therapy, changing the rate of infusion and discontinuing the infusion. If necessary the insulin dose must be adjusted as required.

## 5. INCOMPATIBILITIES

For known incompatibilities of dobutamine solutions with several substances and of sodium metabisulfite see section 6.2 of the Summary of Product Characteristics.

This medicinal product must not be mixed with other medicinal products except with those for which compatibility is proven.

## 6. STORAGE

This medicine does not require any special temperature storage conditions.
Keep the ampoules in the outer carton in order to protect from light.
Do not freeze.

<u>After dilution:</u>
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC.
From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

## Outer Packaging (Carton box)

### 1. NAME OF THE MEDICINAL PRODUCT

**Dobutamine 5 mg/ml solution for infusion**

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 5.6 mg of dobutamine hydrochloride, corresponding to 5 mg of dobutamine.

### 3. LIST OF EXCIPIENTS

Excipients: Sodium metabisulfite (E223), sodium chloride, hydrochloric acid and water for injections.
Please also refer to package leaflet, section 2.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Each 50 ml vial [ampoule] contains 250 mg dobutamine.

250 mg in 50 ml

Ampoules:
1 x 50 ml ampoule
5 x 50 ml ampoules
10 x 50 ml ampoules

Vials:
1 x 50 ml vial
5 x 50 ml vials
10 x 50 ml vials
20 x 50 ml vials

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

This product may need to be diluted.

For intravenous use

Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the vial [ampoule] in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

hameln pharma gmbh
Inselstraße 1
31787 Hameln
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

PL 25215/0004

## 13. BATCH NUMBER

Batch:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

POM

## 15. INSTRUCTIONS ON USE

For single use only. Discard any unused contents.

## 16. INFORMATION IN BRAILLE

Not applicable for products which are only intended for administration by health care professionals *(Guidance concerning the Braille requirement for labelling and the package leaflet; Article 56a of Directive 2001/83/EC as amended).*
*(This sentence will not appear on the printed carton box)*

| Module 1.3.1 | Outer Packaging – UK |
|---|---|

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

GTIN:
SN:

Additional information:

| | |
|---|---|
| Logo MAH: | hameln |
| Distributor: | Distributor<br>hameln pharma ltd<br>Gloucester, UK |

**Outer Packaging (Carton box)**

## 1. NAME OF THE MEDICINAL PRODUCT

**Dobutamine 12.5 mg/ml concentrate for solution for infusion**

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 14 mg of dobutamine hydrochloride, corresponding to 12.5 mg of dobutamine.

## 3. LIST OF EXCIPIENTS

Excipients: Sodium metabisulfite (E223), hydrochloric acid and water for injections.
Please also refer to package leaflet, section 2.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Each 20 ml ampoule contains 250 mg dobutamine.

250 mg in 20 ml

1 x 20 ml ampoule
5 x 20 ml ampoules
50 x 20 ml ampoules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

This product must be diluted.

For intravenous use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the ampoule in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

hameln pharma gmbh
Inselstraße 1
31787 Hameln
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 25215/0003

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

For single use only. Discard any unused contents.

16. INFORMATION IN BRAILLE

Not applicable for products which are only intended for administration by health care professionals *(Guidance concerning the Braille requirement for labelling and the package leaflet; Article 56a of Directive 2001/83/EC as amended).*
*(This sentence will not appear on the printed carton box)*

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

GTIN:
SN:

Additional information:

Logo MAH:

Distributor: Distributor
hameln pharma ltd
Gloucester, UK

## Immediate Packaging (Ampoule/Vial label) – V1

### 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

**Dobutamine 5 mg/ml solution for infusion**

### 2. METHOD OF ADMINISTRATION

For intravenous use
This product may need to be diluted.

### 3. EXPIRY DATE

EXP:

### 4. BATCH NUMBER

Batch:

### 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mg in 50 ml

### 6. OTHER

PL 25215/0004
hameln pharma gmbh

POM

## Immediate Packaging (Ampoule/Vial label) – V2

### 1. NAME OF THE MEDICINAL PRODUCT

**Dobutamine 5 mg/ml solution for infusion**

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 5.6 mg of dobutamine hydrochloride, corresponding to 5 mg of dobutamine.

### 3. LIST OF EXCIPIENTS

Excipients: Sodium metabisulfite (E223), sodium chloride, hydrochloric acid and water for injections.

### 4. PHARMACEUTICAL FORM AND CONTENTS

250 mg in 50 ml

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

This product may need to be diluted.

Forintravenous use

Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

### 8. EXPIRY DATE

EXP:

### 9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the vial [ampoule] in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

hameln pharma gmbh

## 12. MARKETING AUTHORISATION NUMBER(S)

PL 25215/0004

## 13. BATCH NUMBER

Batch:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

POM

## 15. INSTRUCTIONS ON USE

For single use only. Discard any unused contents.

## 16. INFORMATION IN BRAILLE

-

**Immediate Packaging (Ampoule label) – V1**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES(S) OF ADMINISTRATION

**Dobutamine 12.5 mg/ml concentrate for solution for infusion**

2. METHOD OF ADMINISTRATION

For intravenous use

**This product must be diluted.**

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT; BY VOLUME OR BY UNIT

250 mg in 20 ml

6. OTHER

PL 25215/0003

hameln pharma gmbh

POM

**Immediate Packaging (Ampoule label) – V2**

1. NAME OF THE MEDICINAL PRODUCT

**Dobutamine 12.5 mg/ml concentrate for solution for infusion**

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution contains 14 mg of dobutamine hydrochloride, corresponding to 12.5 mg of dobutamine.

3. LIST OF EXCIPIENTS

Excipients: Sodium metabisulfite (E223), hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

250 mg in 20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

This product must be diluted.

For intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Keep the ampoule in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

hameln pharma gmbh

12. MARKETING AUTHORISATION NUMBER(S)

PL 25215/0003

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

For single use only. Discard any unused contents.

16. INFORMATION IN BRAILLE

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Dobutamine 5 mg/ml solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule/vial Dobutamine contains dobutamine hydrochloride corresponding to 250 mg dobutamine.

50 ml ampoule/vial
1 ml contains 5 mg dobutamine.

Excipient with known effect:
This medicine contains 3.06 mg sodium per 1 ml. 50 ml contain 153 mg sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for infusion

The product is a clear, colourless or slightly yellow solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dobutamine is indicated for patients who require a positive inotropic support in the treatment of cardiac decompensation due to depressed contractility.

In cardiogenic shock characterised by heart failure with severe hypotension and in case of septic shock Dobutamine may be useful if added to dopamine in case of disturbed ventricular function, raised filling pressure of the ventricles and raised systemic resistance.

Dobutamine may also be used for detection of myocardial ischaemia and of viable myocardium within the scope of an echocardiographic examination (dobutamine stress echocardiography), if patients cannot undergo a period of exercise or if the exercise yields no information of value.

Paediatric population
Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.”

## 4.2 Posology and method of administration

Posology

**Dobutamine doses must be individually adjusted.**

The required rate of infusion depends on the patient's response to therapy and the adverse reactions experienced.

Dosage in adults:
According to experience, the majority of patients respond to doses of 2.5-10 µg dobutamine/kg/min. In individual cases, doses up to 40 µg dobutamine/kg/min have been administered.

Dosage in paediatric patients:

For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2–20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

**Tables, showing infusion rates with different initial concentrations for various dosages:**

Dosage for infusion delivery systems

One ampoule or vial Dobutamine 5 mg/ml (250 mg in 50 ml) diluted to a solution volume of 500 ml (final concentration 0.5 mg/ml)

| Dosage range | | Specifications in ml/h* (drops/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(drops/min) | 15<br>(5) | 21<br>(7) | 27<br>(9) |
| Medium<br>5 µg/kg/min | ml/h<br>(drops/min) | 30<br>(10) | 42<br>(14) | 54<br>(18) |
| High<br>10 µg/kg/min | ml/h<br>(drops/min) | 60<br>(20) | 84<br>(28) | 108<br>(36) |

* For double concentration, i.e. 500 mg dobutamine added to 500 ml, or 250 mg added to 250 ml solution volume, infusion rates must be halved.

Dosage for syringe pumps

One ampoule or vial Dobutamine 5 mg/ml (250 mg in 50 ml) undiluted (final concentration 5 mg/ml)

| Dosage range | | Specifications in ml/h (ml/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(ml/min) | 1.5<br>(0.025) | 2.1<br>(0.035) | 2.7<br>(0.045) |
| Medium<br>5 µg/kg/min | ml/h<br>(ml/min) | 3.0<br>(0.05) | 4.2<br>(0.07) | 5.4<br>(0.09) |
| High<br>10 µg/kg/min | ml/h<br>(ml/min) | 6.0<br>(0.10) | 8.4<br>(0.14) | 10.8<br>(0.18) |

The chosen syringe pump must be suitable for the volume and rate of administration.

For detailed information about suitable solutions for dilution please see section 6.6.

*Dobutamine stress echocardiography*

Administration in stress echocardiography is undertaken by gradually increasing dobutamine infusion.

The most frequently applied dosage scheme starts with 5 µg/kg/min Dobutamine increased every 3 minutes to 10, 20, 30, 40 µg/kg/min until a diagnostic endpoint (see method and duration of application) is reached.

If no endpoint is reached atropine sulfate may be administered at 0.5 to 2 mg in divided doses of 0.25-0.5 mg at 1 minute intervals to increase the heart rate. Alternatively the infusion rate of dobutamine may be increased to 50 µg/kg/min.

The experience in children and adolescents is limited to the treatment of patients requiring positive inotropic support.

Method of administration

**Dobutamine 5 mg/ml (250 mg in 50 ml) ampoule or vial**
Only for intravenous infusion (syringe pump). Dilution is not required.

Intravenous infusion of dobutamine is also possible after dilution with compatible infusion solutions such as: 5% glucose solution, 0.9% sodium chloride or 0.45% sodium chloride in 5% glucose solution. (For detailed information for dilution please see section 6.6.) Infusion solutions should be prepared immediately before use. (For information on shelf life, see section 6.3.)
Due to its short half-life, dobutamine must be administered as a continuous intravenous infusion.

The dose of dobutamine should be gradually reduced when discontinuing therapy.

The duration of treatment depends on the clinical requirements and is to be determined by the physician and should be as short as possible.

If dobutamine is administered continuously for more than 72 hours, tolerance may occur, requiring an increase in the dose.

During the course of dobutamine administration, heart rate, heart rhythm, blood pressure, diuresis and infusion rate should be closely monitored. Cardiac output, central venous pressure (CVP) and pulmonary capillary pressure (PCP) should be monitored if possible.

Paediatric patients: For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

*Dobutamine stress echocardiography*

For detection of myocardial ischaemia and of viable myocardium dobutamine may only be administered by a physician with sufficient experience in conducting cardiology stress tests. Continuous monitoring of all wall areas via echocardiography, and ECG as well as control of blood pressure is necessary.
Monitoring devices as well as emergency medicines must be available (e.g. defibrillator, I.V. beta-blockers, nitrates, etc.) and staff trained in the resuscitation procedure must be present.

For instructions on dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Dobutamine must not be used in the case of:
- known hypersensitivity to dobutamine or to any of the excipients listed in section 6.1,
- mechanical obstruction of ventricular filling and/or of outflow, such as pericardial tamponade, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, severe aortic stenosis,
- hypovolaemic conditions.

*Dobutamine stress echocardiography*

Dobutamine must not be used for 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 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,
- previous experience of hypersensitivity to dobutamine.

Note:
If administering atropine, the respective contraindications have to be observed.

## 4.4 Special warnings and precautions for use

Dobutamine must not be used for the treatment of patients with bronchial asthma who are hypersensitive to sulfites.

A local increase or decrease of coronary blood flow, which may have an impact on the myocardial oxygen demand, has been observed with dobutamine therapy. The clinical characteristics of patients with severe coronary heart disease may deteriorate, in particular if dobutamine therapy is accompanied by a considerable increase in the heart rate and/or blood pressure. Therefore, as with all positive inotropes, the decision to use dobutamine to treat patients with cardiac ischaemia must be made for each case individually.

Due to the risk of arrhythmias and the uncertainty about long term effects on myocardial dysfunction, inotropic agents, such as dobutamine, should be used with caution in the treatment of Acute Heart Failure (AHF).

As alterations in serum potassium level may occur, the potassium level should be monitored.

If dobutamine is administered continuously for more than 72 hours, tolerance phenomena (tachyphylaxis) may occur, requiring dosage increase.

Precipitous decreases in blood pressure (hypotension) 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 may interfere with HPLC determination of chloramphenicol.

Paediatric population
Dobutamine has been administered to children with low-output hypoperfusion states resulting from decompensated heart failure, cardiac surgery, and cardiogenic and septic shock. Some of the haemodynamic effects of dobutamine hydrochloride may be quantitatively or qualitatively different in children as compared to adults. Increments in heart rate and blood pressure appear to be more frequent and intense in children. Pulmonary wedge pressure may not decrease in children, as it does in adults, or it may actually increase, especially in infants less than one year old. The neonate cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect seems to be more often observed in adult patients than in small children.

Accordingly, the use of dobutamine in children should be monitored closely, bearing in mind these pharmacodynamic characteristics.

*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.

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)x0.85],
- 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 endsystolic volume,
- development of repolarisation abnormality (due to ischaemia horizontal or down sloping 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.

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.

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

This medicinal product contains 3.06 mg **sodium** per 1 ml solution. Each 50 ml ampoule/vial contains 153 mg sodium. This is equivalent to 7.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Dobutamine contains **sodium metabisulfite** (E223), which may rarely cause allergic reactions (hypersensitivity) and asthma-like symptoms (bronchospasm).

**After termination of infusion, patients must be monitored until stabilised.**

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

Via competitive receptor inhibition, the sympathomimetic effect of dobutamine can be reduced by simultaneous administration of a beta receptor blocker. In addition, the alpha agonistic effects may cause peripheral vasoconstriction with a consequent increase in blood pressure.

With simultaneous alpha-receptor blockade, the predominating beta-mimetic effects may cause tachycardia and peripheral vasodilatation.

Simultaneous administration of dobutamine and primarily venous acting vasodilators (e.g. nitrates, sodium nitroprusside) may cause a greater increase of cardiac output as well as a more pronounced decrease of peripheral resistance and ventricular filling pressure than administration of one of the individual substances alone.

Administering dobutamine to diabetic patients may cause increased insulin demand. In diabetic patients insulin levels should be checked when starting dobutamine therapy, changing the rate of infusion and discontinuing the infusion. If necessary the insulin dose must be adjusted as required.

Simultaneous administration of high doses of dobutamine with ACE inhibitors (e.g. captopril) may cause an increase in cardiac output, accompanied by increased myocardial oxygen consumption. Chest pain and rhythm disturbances have been reported in this context.

Dobutamine combined with dopamine causes – depending on the dopamine dosage and in contrast to its sole administration – a more distinct increase of blood pressure as well as a decrease or no change of ventricular filling pressure.

Sodium metabisulfite is a very reactive compound. It must therefore be assumed that thiamine (vitamin $B_1$) co-administered with the preparation is catabolised.

Caution should be exercised when administering dobutamine with inhaled anaesthetics, since concomitant use may increase the excitability of the myocardium and the risk of ventricular extrasystoles.

*Dobutamine stress echocardiography*

In the case of anti-anginal therapy, in particular heart rate lowering agents like beta-blockers, the ischaemic reaction to stress is less pronounced or may be nonexistent. Therefore anti-anginal therapy may need to be withheld for 12 hours prior to dobutamine stress echocardiography.

When adding atropine at the highest titration level of dobutamine:
Due to the prolonged duration of the stress echocardiography protocol, the higher total dose of dobutamine and the simultaneous administration of atropine, there is an increased risk of adverse reactions.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
As there is no adequate data on the safety of dobutamine in human pregnancy and it is not known whether dobutamine crosses the placenta, dobutamine should not be used during pregnancy unless potential benefits outweigh the potential risks to the foetus and there are no safer therapeutic alternatives.

Breastfeeding
It is not known, whether dobutamine is excreted in breast milk, so caution should be exercised. If treatment with dobutamine is required for the mother during lactation, breast feeding should be discontinued for the duration of treatment.

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable 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 |

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. |

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.<br>Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles.<br>Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised prior to dobutamine infusion.<br>Vasoconstriction in particular in patients who have previously been treated with beta blockers.<br>Anginal pain, palpitations. |
| Uncommon: | Ventricular tachycardia, ventricular fibrillation. |
| Very rare: | Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest. |
| Not known: | Decrease in pulmonary capillary pressure. |

Paediatric population

The undesirable effects include elevation of systolic blood pressure, systemic hypertension or hypotension, tachycardia, headache, and elevation of pulmonary wedge pressure leading to pulmonary congestion and edema, and symptomatic complaints.

*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 second degree atrioventricular block, coronary vasospasms.<br>Hypertensive/hypotensive blood pressure decompensation, occurrence of intracavitary pressure gradients, palpitations. |
| Not known: | Stress cardiomyopathy (Takotsubo syndrome) (see section 4.4). |

Respiratory, 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. |

Further undesirable effects
Restlessness, nausea, headache, paraesthesia, tremor, urinary urgency, feeling of heat and anxiety, myoclonic spasm.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Symptoms of overdose
Symptoms are generally caused by excessive stimulation of beta-receptors. Symptoms may include nausea, vomiting, anorexia, tremor, anxiety, palpitations, headache, anginal pain and unspecific chest pain. The positive inotropic and chronotropic cardiac effects may cause hypertension, supraventricular/ventricular arrhythmia and even ventricular fibrillation as well as myocardial ischaemia. Hypotension may occur due to peripheral vasodilatation.

Treatment of overdose
Dobutamine is metabolised rapidly and has a short duration of effect (half-life 2 - 3 minutes).

In case of overdose, administration of dobutamine should be terminated. If necessary, resuscitation procedures must be carried out immediately. Under conditions of intensive care, vital parameters must be monitored and corrected if necessary. Balanced levels of blood gases and serum electrolytes must be maintained.

Severe ventricular arrhythmias can be treated with administration of lidocaine or a beta blocker (e. g. propranolol).

Angina pectoris should be treated with a sublingually administrated nitrate or possibly a short-acting, I.V. beta blocker (e.g. esmolol).

In case of a hypertensive reaction, dose reduction or termination of the infusion is usually sufficient.

With oral administration, the quantity absorbed from the mouth or gastrointestinal tract is unpredictable. In case of accidental oral administration, resorption may be reduced by administration of activated charcoal, which is often more effective than administration of emetics or performing gastric lavage.

The benefit of forced diuresis, peritoneal dialysis, haemodialysis or haemoperfusion via activated charcoal has not been demonstrated for cases of dobutamine overdosage.

*Dobutamine stress echocardiography*

If applying one of the common dosage schemes, toxic doses are not reached, not even cumulatively. In case of severe complications during diagnostic administration of dobutamine, the infusion must be terminated at once and sufficient oxygen supply and ventilation must be guaranteed. Treatment of angina pectoris should be performed with an intravenous beta-blocker with a very short-acting effect. Angina pectoris may also be treated with a sublingually administered nitrate, if necessary. Class I and III antiarrhythmics must not be administrated.

# 5 PHARMACOLOGICAL PROPERTIES

## 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 $beta_1$-receptors but also on cardiac $alpha_1$-receptors; which leads to increased contractility with an increase in stroke volume and cardiac output. Dobutamine also has an agonistic effect on peripheral $beta_2$- receptors and to a smaller extent on peripheral $alpha_2$-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. Half-life is 2 - 3 minutes, distribution volume is 0.2 l/kg, plasma clearance is not dependent on cardiac output and is 2.4 l/min/$m^2$. Dobutamine is mainly metabolised in the tissue and liver. It is mainly metabolised to conjugated glucuronides as well as the pharmacologically inactive 3-O-methyldobutamine. 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 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 metabisulfite (E223)
Sodium chloride
Hydrochloric acid
Water for injections

### 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,
- cephalotine 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

3 years.

After first opening/dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC. 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 2ºC to 8ºC unless preparation has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Keep the ampoules/vials in the outer carton in order to protect from light.
This medicine does not require any special temperature storage conditions.
Do not freeze.

For storage conditions after first opening/dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Dobutamine 5 mg/ml (250 mg in 50 ml) ampoules made of colourless, neutral glass, type I Ph.Eur.
1, 5 and 10 ampoules with 50 ml solution for infusion.

Dobutamine 5 mg/ml (250 mg in 50 ml) vials made of colourless, neutral glass, type I Ph. Eur, with rubber stopper, Ph.Eur.
1, 5, 10 and 20 vials with 50 ml solution for infusion.

Not all pack sizes may be marketed.

## 6.6 Special precautions for 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 AUTHORISATION HOLDER

hameln pharma gmbh
Inselstraße 1
31787 Hameln, Germany

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 25215/0004

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2006 / 13/02/2011

## 10 DATE OF REVISION OF THE TEXT

24/02/2022

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Dobutamine 12.5 mg/ml concentrate for solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule Dobutamine contains dobutamine hydrochloride corresponding to 250 mg dobutamine.

20 ml ampoule
1 ml contains 12.5 mg dobutamine.

Excipient with known effect:
This medicine contains less than 1mmol sodium (23 mg) per 20 ml, that is to say essentially `sodium-free´.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

The product is a clear, colourless or slightly yellow solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Dobutamine is indicated for patients who require a positive inotropic support in the treatment of cardiac decompensation due to depressed contractility.

In cardiogenic shock characterised by heart failure with severe hypotension and in case of septic shock Dobutamine may be useful if added to dopamine in case of disturbed ventricular function, raised filling pressure of the ventricles and raised systemic resistance.

Dobutamine may also be used for detection of myocardial ischaemia and of viable myocardium within the scope of an echocardiographic examination (dobutamine stress echocardiography), if patients cannot undergo a period of exercise or if the exercise yields no information of value.

Paediatric population
Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.”

## 4.2 Posology and method of administration

Posology

**Dobutamine doses must be individually adjusted.**

The required rate of infusion depends on the patient's response to therapy and the adverse reactions experienced.

Dosage in adults:
According to experience, the majority of patients respond to doses of 2.5-10 µg dobutamine/kg/min. In individual cases, doses up to 40 µg dobutamine/kg/min have been administered.

Dosage in paediatric patients:

For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2– 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1.0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller "therapeutic width" in children.

**Tables, showing infusion rates with different initial concentrations for various dosages:**

Dosage for infusion delivery systems

One ampoule Dobutamine 12.5 mg/ml (250 mg in 20 ml) diluted to a solution volume of 500 ml (final concentration 0.5 mg/ml)

| Dosage range | | Specifications in ml/h* (drops/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(drops/min) | 15<br>(5) | 21<br>(7) | 27<br>(9) |
| Medium<br>5 µg/kg/min | ml/h<br>(drops/min) | 30<br>(10) | 42<br>(14) | 54<br>(18) |
| High<br>10 µg/kg/min | ml/h<br>(drops/min) | 60<br>(20) | 84<br>(28) | 108<br>(36) |

* For double concentration, i.e. 500 mg dobutamine added to 500 ml, or 250 mg added to 250 ml solution volume, infusion rates must be halved.

Dosage for syringe pumps

One ampoule Dobutamine 12.5 mg/ml (250 mg in 20 ml) diluted to a solution volume of 50 ml (final concentration 5 mg/ml)

| Dosage range | | Specifications in ml/h (ml/min) | | |
|---|---|---|---|---|
| | | Patient's weight | | |
| | | 50 kg | 70 kg | 90 kg |
| Low<br>2.5 µg/kg/min | ml/h<br>(ml/min) | 1.5<br>(0.025) | 2.1<br>(0.035) | 2.7<br>(0.045) |
| Medium<br>5 µg/kg/min | ml/h<br>(ml/min) | 3.0<br>(0.05) | 4.2<br>(0.07) | 5.4<br>(0.09) |
| High<br>10 µg/kg/min | ml/h<br>(ml/min) | 6.0<br>(0.10) | 8.4<br>(0.14) | 10.8<br>(0.18) |

The chosen syringe pump must be suitable for the volume and rate of administration.

For detailed information about suitable solutions for dilution please see section 6.6.

*Dobutamine stress echocardiography*

Administration in stress echocardiography is undertaken by gradually increasing dobutamine infusion.

The most frequently applied dosage scheme starts with 5 µg/kg/min Dobutamine increased every 3 minutes to 10, 20, 30, 40 µg/kg/min until a diagnostic endpoint (see method and duration of application) is reached.
If no endpoint is reached atropine sulfate may be administered at 0.5 to 2 mg in divided doses of 0.25-0.5 mg at 1 minute intervals to increase the heart rate. Alternatively the infusion rate of dobutamine may be increased to 50 µg/kg/min.

The experience in children and adolescents is limited to the treatment of patients requiring positive inotropic support.

Method of administration

**Dobutamine 12.5 mg/ml (250 mg in 20 ml)**
The infusion solution concentrate must be diluted before administration. Only for intravenous infusion.

Intravenous infusion of dobutamine is possible after dilution with compatible infusion solutions such as: 5% glucose solution, 0.9% sodium chloride or 0.45% sodium chloride in 5% glucose solution. (For detailed information for dilution please see section 6.6.) Infusion solutions should be prepared immediately before use. (For information on shelf life, see section 6.3.)

Due to its short half-life, dobutamine must be administered as a continuous intravenous infusion.

The dose of dobutamine should be gradually reduced when discontinuing therapy.

The duration of treatment depends on the clinical requirements and is to be determined by the physician and should be as short as possible.

If dobutamine is administered continuously for more than 72 hours, tolerance may occur, requiring an increase in the dose.

During the course of dobutamine administration, heart rate, heart rhythm, blood pressure, diuresis and infusion rate should be closely monitored. Cardiac output, central venous pressure (CVP) and pulmonary capillary pressure (PCP) should be monitored if possible.

Paediatric patients: For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

*Dobutamine stress echocardiography*

For detection of myocardial ischaemia and of viable myocardium dobutamine may only be administered by a physician with sufficient experience in conducting cardiology stress tests. Continuous monitoring of all wall areas via echocardiography, and ECG as well as control of blood pressure is necessary.

Monitoring devices as well as emergency medicines must be available (e.g. defibrillator, I.V. beta-blockers, nitrates, etc.) and staff trained in the resuscitation procedure must be present.

For instructions on dilution of the medicinal product before administration, see section 6.6

## 4.3 Contraindications

Dobutamine must not be used in the case of:

- hypersensitivity to the active substance dobutamine or to any of the excipients listed in section 6.1,
- mechanical obstruction of ventricular filling and/or of outflow, such as pericardial tamponade, constrictive pericarditis, hypertrophic obstructive cardiomyopathy, severe aortic stenosis,
- hypovolaemic conditions.

*Dobutamine stress echocardiography*

Dobutamine must not be used for 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 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,
- previous experience of hypersensitivity to dobutamine.

Note:

If administering atropine, the respective contraindications have to be observed.

## 4.4 Special warnings and precautions for use

Dobutamine must not be used for the treatment of patients with bronchial asthma who are hypersensitive to sulfites.

A local increase or decrease of coronary blood flow, which may have an impact on the myocardial oxygen demand, has been observed with dobutamine therapy. The clinical characteristics of patients with severe coronary heart disease may deteriorate, in particular if dobutamine therapy is accompanied by a considerable increase in the heart rate and/or blood pressure. Therefore, as with all positive inotropes, the decision to use dobutamine to treat patients with cardiac ischaemia must be made for each case individually.

Due to the risk of arrhythmias and the uncertainty about long term effects on myocardial dysfunction, inotropic agents, such as dobutamine, should be used with caution in the treatment of Acute Heart Failure (AHF).

As alterations in serum potassium level may occur, the potassium level should be monitored.

If dobutamine is administered continuously for more than 72 hours, tolerance phenomena (tachyphylaxis) may occur, requiring dosage increase.

Precipitous decreases in blood pressure (hypotension) 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 may interfere with HPLC determination of chloramphenicol.

Paediatric population

Dobutamine has been administered to children with low-output hypoperfusion states resulting from decompensated heart failure, cardiac surgery, and cardiogenic and septic shock. Some of the haemodynamic effects of dobutamine hydrochloride may be quantitatively or qualitatively different in children as compared to adults. Increments in heart rate and blood pressure appear to be more frequent and intense in children. Pulmonary wedge pressure may not decrease in children, as it does in adults, or it may actually increase, especially in infants less than one year old. The

neonate cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect seems to be more often observed in adult patients than in small children.

Accordingly, the use of dobutamine in children should be monitored closely, bearing in mind these pharmacodynamic characteristics.

*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.

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)x0.85],
- 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 endsystolic volume,
- development of repolarisation abnormality (due to ischaemia horizontal or down sloping 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.

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.

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

Dobutamine contains **sodium metabisulfite** (E223), which may rarely cause allergic reactions (hypersensitivity) and asthma-like symptoms (bronchospasm).

**After termination of infusion, patients must be monitored until stabilised.**

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

Via competitive receptor inhibition, the sympathomimetic effect of dobutamine can be reduced by simultaneous administration of a beta receptor blocker. In addition, the alpha agonistic effects may cause peripheral vasoconstriction with a consequent increase in blood pressure.

With simultaneous alpha-receptor blockade, the predominating beta-mimetic effects may cause tachycardia and peripheral vasodilatation.

Simultaneous administration of dobutamine and primarily venous acting vasodilators (e.g. nitrates, sodium nitroprusside) may cause a greater increase of cardiac output as well as a more pronounced decrease of peripheral resistance and ventricular filling pressure than administration of one of the individual substances alone.

Administering dobutamine to diabetic patients may cause increased insulin demand. In diabetic patients insulin levels should be checked when starting dobutamine therapy changing the rate of infusion and discontinuing the infusion. If necessary the insulin dose must be adjusted as required.

Simultaneous administration of high doses of dobutamine with ACE inhibitors (e.g. captopril) may cause an increase in cardiac output, accompanied by increased myocardial oxygen consumption. Chest pain and rhythm disturbances have been reported in this context.

Dobutamine combined with dopamine causes – depending on the dopamine dosage and in contrast to its sole administration – a more distinct increase of blood pressure as well as a decrease or no change of ventricular filling pressure.

Sodium metabisulfite is a very reactive compound. It must therefore be assumed that thiamine (vitamin $B_1$) co-administered with the preparation is catabolised.

Caution should be exercised when administering dobutamine with inhaled anaesthetics, since, concomitant use may increase the excitability of the myocardium and the risk of ventricular extrasystoles.

*Dobutamine stress echocardiography*

In the case of anti-anginal therapy, in particular heart rate lowering agents like beta-blockers, the ischaemic reaction to stress is less pronounced or may be nonexistent.

Therefore anti-anginal therapy may need to be withheld for 12 hours prior to dobutamine stress echocardiography.

When adding atropine at the highest titration level of dobutamine:

Due to the prolonged duration of the stress echocardiography protocol, the higher total dose of dobutamine and the simultaneous administration of atropine, there is an increased risk of adverse reactions.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

As there is no adequate data on the safety of dobutamine in human pregnancy and it is not known whether dobutamine crosses the placenta, dobutamine should not be used during pregnancy unless potential benefits outweigh the potential risks to the foetus and there are no safer therapeutic alternatives.

Breastfeeding

It is not known, whether dobutamine is excreted in breast milk, so caution should be exercised. If treatment with dobutamine is required for the mother during lactation, breast feeding should be discontinued for the duration of treatment.

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable 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 |

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. |

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.<br>Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles.<br>Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised prior to dobutamine infusion.<br>Vasoconstriction in particular in patients who have previously been treated with beta blockers.<br>Anginal pain, palpitations. |
| Uncommon: | Ventricular tachycardia, ventricular fibrillation. |
| Very rare: | Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest. |
| Not known: | Decrease in pulmonary capillary pressure. |

Paediatric population

The undesirable effects include elevation of systolic blood pressure, systemic hypertension or hypotension, tachycardia, headache, and elevation of pulmonary wedge pressure leading to pulmonary congestion and edema, and symptomatic complaints.

*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 second degree atrioventricular block, coronary vasospasms. |

| | |
|---|---|
| | Hypertensive/hypotensive blood pressure decompensation, occurrence of intracavitary pressure gradients, palpitations. |
| Not known: | Stress cardiomyopathy (Takotsubo syndrome) (see section 4.4). |

Respiratory, 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. |

Further undesirable effects

Restlessness, nausea, headache, paraesthesia, tremor, urinary urgency, feeling of heat and anxiety, myoclonic spasm.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Symptoms of overdose

Symptoms are generally caused by excessive stimulation of beta-receptors. Symptoms may include nausea, vomiting, anorexia, tremor, anxiety, palpitations, headache, anginal pain and unspecific chest pain. The positive inotropic and chronotropic cardiac effects may cause hypertension, supraventricular/ventricular arrhythmia and even ventricular fibrillation as well as myocardial ischaemia. Hypotension may occur due to peripheral vasodilatation.

Treatment of overdose

Dobutamine is metabolised rapidly and has a short duration of effect (half-life 2 - 3 minutes).

In case of overdose, administration of dobutamine should be terminated. If necessary, resuscitation procedures must be carried out immediately. Under conditions of intensive care, vital parameters must be monitored and corrected if

necessary. Balanced levels of blood gases and serum electrolytes must be maintained.

Severe ventricular arrhythmias can be treated with administration of lidocaine or a beta blocker (e. g. propranolol).

Angina pectoris should be treated with a sublingually administrated nitrate or possibly a short-acting, I.V. beta blocker (e.g. esmolol).

In case of a hypertensive reaction, dose reduction or termination of the infusion is usually sufficient.

With oral administration, the quantity absorbed from the mouth or gastrointestinal tract is unpredictable. In case of accidental oral administration, resorption may be reduced by administration of activated charcoal, which is often more effective than administration of emetics or performing gastric lavage.

The benefit of forced diuresis, peritoneal dialysis, haemodialysis or haemoperfusion via activated charcoal has not been demonstrated for cases of dobutamine overdosage.

*Dobutamine stress echocardiography*

If applying one of the common dosage schemes, toxic doses are not reached, not even cumulatively. In case of severe complications during diagnostic administration of dobutamine, the infusion must be terminated at once and sufficient oxygen supply and ventilation must be guaranteed. Treatment of angina pectoris should be performed with an intravenous beta-blocker with a very short-acting effect. Angina pectoris may also be treated with a sublingually administered nitrate, if necessary. Class I and III antiarrhythmics must not be administrated.

# 5 PHARMACOLOGICAL PROPERTIES

## 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 $beta_1$-receptors but also on cardiac $alpha_1$-receptors; which leads to increased contractility with an increase in stroke volume and cardiac output. Dobutamine also has an agonistic effect on peripheral $beta_2$- receptors and to a smaller extent on peripheral $alpha_2$-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. Half-life is 2 - 3 minutes, distribution volume is 0.2 l/kg, plasma clearance is not dependent on cardiac output and is 2.4 l/min/$m^2$. Dobutamine is mainly metabolised in the tissue and liver. It is mainly metabolised to conjugated glucuronides as well as the pharmacologically inactive 3-O-methyldobutamine. 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 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 metabisulfite (E223)
Hydrochloric acid
Water for injections

## 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,
- cephalotine 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

3 years.

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.

## 6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.
This medicine does not require any special temperature storage conditions.
Do not freeze.

For storage conditions after first opening/dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Dobutamine 12.5 mg/ml (250 mg in 20 ml)
1, 5 and 50 ampoules made of colourless, neutral glass, type I Ph.Eur, with 20 ml concentrate for solution for infusion.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Prior to administration the concentrate for solution for infusion must be diluted to a volume of 50 ml or more. For full preparation instructions please see section 4.2.

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 AUTHORISATION HOLDER

hameln pharma gmbh
Inselstraße 1
31787 Hameln, Germany

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 25215/0003

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2011

## 10 DATE OF REVISION OF THE TEXT

24/02/2022