



hameln pharma gmbh  
Inselstraße 1  
31787 Hameln

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

**Antrag vom 06.09.2022 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  
gemäß § 4 Absatz 5 Medizinischer Bedarf Versorgungssicherstellungsverordnung  
(MedBVS)**

<b>Arzneimittelbezeichnung</b>	<b>Zulassungsinhaber</b>	<b>Zulassungsnummer</b>
<b>Dobutamin-hameln 12,5 mg/ml</b>	<b>hameln pharma gmbh</b>	<b>51613.01.00</b>

**Wirkstoff: Dobutamin**

Sehr geehrte Damen und Herren,  
auf Ihren mit E-Mail vom 06. September 2022 gestellten Antrag ergeht folgender

**BESCHEID:**

1. Es wird im Einzelfall gestattet, dass das o. g. Arzneimittel mit der für den britischen Markt bestimmten und damit mit einer in einer anderen als der deutschen Sprache verfassten Kennzeichnung und Packungsbeilage in den Verkehr gebracht wird.
2. Ergänzend wird ausnahmsweise abweichend von §§ 22, 24 AMG zugelassen, dass die der britischen Zulassung entsprechende Ware in Deutschland mit nicht den aktuellen Zulassungsunterlagen entsprechenden Informationstexten, Herstellungs- und Endproduktspezifikationen in Verkehr gebracht wird. Diese Ausnahme gilt nur unter der Bedingung, dass nach Deutschland verbrachte Chargen in Hinblick auf das

Verunreinigungsprofil der Spezifikation der aktuell in Deutschland gültigen Zulassung entsprechen.

3. Diese Gestattung ist befristet bis zum 30. November 2022 und wird unter dem Vorbehalt des jederzeitigen Widerrufs erteilt.

### 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 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 Kreislauf-funktion unterschiedliche pharmakologische Charakteristika. So eignen sich weitere Substanzen der Substanzklasse nicht ausreichend und können nicht deckungsgleich zu Dobutamin eingesetzt werden.

Zu 2.

Die zugelassene Ausnahme zur Abweichung von der erteilten Zulassung stützt sich auf § 4 Absatz 5 MedBVS. Nach dieser Vorschrift kann die nach § 77 AMG zuständige Bundesoberbehörde im Einzelfall Ausnahmen von bestimmten Vorschriften des Vierten Abschnittes des AMG zulassen, wenn dies nach Vornahme einer Nutzen-Risiko-Bewertung zur Sicherstellung der Versorgung der Bevölkerung mit Arzneimitteln erforderlich ist. Diese Voraussetzung ist hier erfüllt.

Die Ware in englischer Aufmachung unterscheidet sich zu den aktuellen Zulassungsunterlagen darin, dass abweichende inerte Gase als Hilfsstoffe zur Begasung und abweichende Hilfsstoffe zur pH-Werteinstellung verwendet wurden. Zudem weicht die zugrundeliegende Spezifikation und der Produktinformationstext von der aktuell gültigen Zulassung ab.

Die erfolgte Nutzen-Risiko-Bewertung kommt zu dem Schluss, dass der Nutzen, wie oben unter Ziffer 1 dargelegt, gegeben ist. Ein eventuelles Risiko wird innerhalb der unterschiedlichen Spezifikationen der Verunreinigungen erkannt, weshalb jede nach Deutschland verbrachte Charge der hier gemäß aktueller Zulassung gültigen Spezifikation, vor allem hinsichtlich der Verunreinigungen, entsprechen muss, was durch die gleichzeitig angeordnete Bedingung sichergestellt ist.

Zu 3.

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.

Der Widerrufsvorbehalt stützt sich auf § 36 Absatz 2 Nr. 3 VwVfG, wonach ein Verwaltungsakt nach pflichtgemäßem Ermessen auch mit einem Vorbehalt des Widerrufs erlassen werden kann. Dieser Vorbehalt ist notwendig und zugleich das mildeste Mittel, um angemessen reagieren zu können, sofern sich herausstellen sollte, dass die Voraussetzungen für die Ausnahme nicht mehr vorliegen oder die Sicherheit von Patientinnen und Patienten durch die zugelassenen Abweichungen von den üblichen Zulassungen beeinträchtigt werden sollte.

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 08.09.2022

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 patient**

### **Dobutamine 12.5 mg/ml concentrate for 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Dobutamine 12.5 mg/ml concentrate for solution for infusion, which will be referred to as Dobutamine Concentrate throughout this leaflet.

#### What is in this leaflet

1. What Dobutamine Concentrate is and what it is used for
2. What you need to know before you are given Dobutamine Concentrate
3. How Dobutamine Concentrate is given
4. Possible side effects
5. How to store Dobutamine Concentrate
6. Contents of the pack and other information

#### 1. What Dobutamine Concentrate is and what it is used for

Dobutamine Concentrate belongs to a group of medicines known as inotropes, which make your heart beat more strongly.

In adults it is used:

- in open heart surgery
- to treat heart disease
- to treat heart failure
- in shock
- as an alternative to exercise for stress testing the heart.

#### 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 are given Dobutamine Concentrate

**You should not be given Dobutamine Concentrate if you:**

- are allergic to Dobutamine, sodium metabisulfite or any of the other ingredients in this injection.
- suffer from high blood pressure due to a tumour near the kidney (Pheochromocytoma).
- have certain heart or blood vessel disorders. Dobutamine should not be used to detect poor blood supply to your heart (a cardiac stress test known as Dobutamine Stress Echocardiography)

#### **Warnings and precautions:**

Talk to your doctor or nurse if you have any of the following conditions:

- have recently had a heart attack
- have had a heart transplant
- are asthmatic
- have unstable angina
- have heart disease
- have high blood pressure
- have any condition that would make **exercise** dangerous for you.

#### 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.

#### **Other medicines and Dobutamine Concentrate:**

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This is especially important with the following medicines as they may interact with your Dobutamine Concentrate:

- beta blockers (medicines used to relieve certain heart conditions, anxiety and migraine).
- anaesthetics.

- entacapone (a medicine to treat Parkinson's Disease).

**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 taking this medicine.

**Driving and using machines:**

You should not drive or use machinery if you are affected by the administration of Dobutamine Concentrate.

**3. How Dobutamine Concentrate is given**

Your nurse or doctor will give you the injection.

Your doctor will decide the correct dosage for you and how and when the injection will be given.

Since the injection will be given to you by a doctor or nurse, it is unlikely that you will be given too much. If you think you have been given too much, feel sick, are sick, feel anxious, feel palpitations, have a headache, feel short of breath or have chest pain you must tell the person giving you the injection.

**Use in Children**

Your child will be given the injection by a nurse or doctor who will decide the correct dosage for your child and how **and** when the injection will be given.

If you have any further questions or concerns on the use of this medicine for your child ask the doctor or nurse giving the injection.

**4. Possible side effects**

Like all medicines, Dobutamine Concentrate can cause side effects, although not everybody gets them.

Your doctor will examine your heart before giving you Dobutamine Concentrate to decide if you are suitable to receive the drug.

The following side-effects have been reported:

**Very common (more than 1 in 10 patients)**

- increased heart rate
- chest pain
- heartbeat disturbances

**Common (in less than 1 in 10, but more than 1 in 100 patients)**

- blood pressure increase or decrease
- narrowing of the blood vessels (vasoconstriction)
- irregular heartbeat (palpitations)
- asthma-like symptoms (bronchospasm)
- shortness of breath
- increase in white blood cells (eosinophilia)
- inhibition of blood clot formation
- rash (exanthema)
- fever
- inflammation of the vein at the injection site (phlebitis)

**Uncommon (in less than 1 in 100, but more than 1 in 1000 patients)**

- fast contractions of the ventricles of the heart (ventricular tachycardia)
- uncontrolled contractions of the ventricles of the heart (ventricular fibrillation)
- heart attack (myocardial infarction)

**Very rare (in less than 1 in 10 000, including isolated cases)**

- 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)

**Not known (cannot be estimated from the available data)**

- chest pain caused by stress (stress cardiomyopathy)
- allergic reactions (hypersensitivity reactions) including symptoms of rash, fever, increase in white blood cells (eosinophilia) and asthma-like symptoms (bronchospasm)
- severe allergic reactions (anaphylactic reactions) and severe life-threatening asthmatic episodes possibly due to sensitivity to sodium metabisulfite (see Section 2)
- muscle cramp (myoclonus) in patients with severe renal failure receiving dobutamine
- abnormal heart function test (electrocardiogram ST segment elevation)
- inflammation of heart muscle (eosinophilic myocarditis) in heart transplant patients
- heart block (left ventricular outflow tract obstruction)
- fatal heart rupture
- restlessness
- feeling sick (nausea)

- headache
- pins and needles (paraesthesia)
- tremor
- increased desire to urinate (at high doses)
- feelings of heat and anxiety
- muscle cramp (myoclonic spasm)
- 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.

#### **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](http://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 Concentrate**

Your doctor and pharmacist are responsible for the correct storage, use and disposal of this medicine.

- 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 carton/label. The expiry date refers to the last day of the month.
- Do not use this medicine if you notice the solution is not clear and free of particles or if the container is damaged.
- Your pharmacist will dispose of any medicine that remains unused.

#### **6. Contents of the pack and other information**

##### **What Dobutamine Concentrate contains:**

The active ingredient is dobutamine hydrochloride. Each 1 ml contains dobutamine hydrochloride equivalent to 12.5 mg dobutamine in a sterile solution for injection.

The other **ingredients** are sodium metabisulfite, sodium hydroxide, hydrochloric acid, sterile water for injections and carbon dioxide.

##### **What Dobutamine Concentrate looks like and contents of the pack:**

Dobutamine Concentrate is supplied in 20 ml clear glass ampoules, in cartons containing one, five or ten ampoules. Not all sizes may be marketed.

The marketing authorisation number of this medicine is: PL 01502/0054.

##### **Marketing Authorisation Holder:**

hameln pharma ltd  
Nexus, Gloucester Business Park,  
Gloucester, GL3 4AG  
United Kingdom

##### **Manufacturer:**

Siegfried Hameln GmbH  
Langes Feld 13  
31789 Hameln  
Germany

hameln rds s.r.o.  
Horná 36  
900 01 Modra  
Slovak Republic

##### **For any information about this medicine, please contact the Marketing Authorisation Holder**

This leaflet was last revised in February 2022

141x55x145

250 mg in 20 ml

# DOBUTamine

12.5 mg/ml concentrate  
for solution for infusion

250 mg in 20 ml

10 x 20 ml ampoules.  
For i.v. infusion only.

250 mg in 20 ml

# DOBUTamine

12.5 mg/ml concentrate  
for solution for infusion

1 ml solution concentrate for infusion contains:

ACTIVE INGREDIENT:  
Dobutamine hydrochloride 14 mg  
corresponding to dobutamine 12.5 mg

PRESERVATIVE:  
Sodium metabisulfite 0.15 mg

Excipients: Sodium hydroxide, hydrochloric acid, carbon dioxide and water for injections.

Read package leaflet before use.

Must not be diluted with bicarbonate or other alkaline solution. If not required immediately, the diluted solution may be stored for up to 24 hours in a refrigerator.

If only part used discard the remaining solution.

Keep out of the sight and reach of children.

**Do not store above 25°C.**

Keep container in the outer carton in order to protect from light.

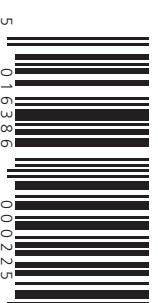
hameln pharma ltd

Gloucester

UK

PL 01502/0054

POM



# DOBUTamine

12.5 mg/ml concentrate  
for solution for infusion

250 mg in 20 ml

10 x 20 ml ampoules.  
For i.v. infusion only.

**hameln**

64475/09/20

**This product must be diluted to at least 50 ml, with a suitable diluent, before use.**

10 ampoules each containing 20 ml concentrate for i.v. infusion.

250 mg in 20 ml

# DOBUTamine

12.5 mg/ml concentrate  
for solution for infusion

250 mg in 20 ml

10 x 20 ml ampoules.  
For i.v. infusion only.

# DOBUTamine

12.5 mg/ml concentrate  
for solution for infusion

250 mg in 20 ml

250 mg in 20 ml

Varnish free field for 2D Barcode and Associated information

GTIN:  
SN:  
Batch:  
EXP:



# hameln

hameln pharma ltd

Nexus, Gloucester Business Park, Gloucester, GL3 4AG, UK

Tel.: +44 (0)1452 621661


Fax: +44 (0)1452 632732

Web: www.hameln.co.uk

Email: enquires@hameln.co.uk

Artwork code:	64475/09/20
Date last revised:	26/02/2020
Last revised by:	J.Jones
Customer	hameln pharma ltd
Country	UK
Language:	English
Product:	<b>Dobutamine 12.5 mg/ml</b>
Component:	Carton 10 x 20ml
Dimensions:	141 x 55 x 145 mm
Software:	Adobe Illustrator CC
Font(s):	Frutiger light, bold
Colour:	Schwarz, P 259 C, P 185 C
Signature:	





**250 mg in 20 ml**

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

**250 mg in 20 ml**

For i.v. infusion only.

**This product must be diluted  
to at least 50 ml, with a  
suitable diluent, before use.**

PL 01502/0054  
hameln pharma ltd  
43822/09/20

Batch:  
EXP:

POM



# hameln

**hameln pharma ltd**

Nexus, Gloucester Business Park, Gloucester, GL3 4AG, UK  
 Tel.: +44 (0)1452 621661  
 Fax: +44 (0)1452 632732  
 Web: www.hameln.co.uk  
 Email: enquiries@hameln.co.uk

<b>Artwork code:</b>	43822/09/20
<b>Date last revised:</b>	26.02.2020
<b>Last revised by:</b>	J.Jones
<b>Customer</b>	hameln pharma ltd
<b>Country</b>	UK
<b>Language:</b>	English
<b>Product:</b>	Dobutamine Conc.
<b>Component:</b>	Label 20ml
<b>Dimensions:</b>	60 x 45 mm
<b>Software:</b>	Adobe Illustrator CC
<b>Font(s):</b>	Frutiger light, bold
<b>Colour:</b>	schwarz, P 259 C, P 185 C
<b>Signature:</b>	

## **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 ml contains Dobutamine Hydrochloride USP equivalent to Dobutamine 12.5 mg.

Each ampoule contains 250 mg Dobutamine in 20ml.

### **3. PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

##### *Adult population*

Dobutamine 12.5 mg/ml concentrate for solution for infusion is indicated in adults who require inotropic support in the treatment of low output cardiac failure associated with myocardial infarction, open heart surgery, cardiomyopathies, septic shock and cardiogenic shock. Dobutamine 12.5 mg/ml concentrate for solution for infusion can also increase or maintain cardiac output during positive end expiratory pressure (PEEP) ventilation.

##### *Dobutamine stress echocardiography (Adult population only)*

Dobutamine 12.5 mg/ml concentrate for solution for infusion may also be used for cardiac stress testing as an alternative to exercise in patients for whom routine exercise cannot be satisfactorily performed. This use of dobutamine should only be undertaken in units which already perform exercise stress testing and all normal care and precautions required for such testing are also required when using dobutamine for this purpose.

##### *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**

Route of Administration: For intravenous use only.

### ***Adult population***

Dobutamine 12.5 mg/ml concentrate for solution for infusion must be diluted to at least 50 ml prior to administration in an IV container with one of the intravenous solutions listed below:

Sodium Chloride Intravenous Infusion BP

5% Dextrose Intravenous Infusion BP

5% Dextrose + 0.9% Sodium Chloride Intravenous Infusion BP

5% Dextrose + 0.45% Sodium Chloride Intravenous Infusion BP

Sodium Lactate Intravenous Infusion BP

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

250 ml contains 1,000 micrograms/ml of dobutamine

500 ml contains 500 micrograms/ml of dobutamine

**The prepared solution should be used within 24 hours.**

### Method of administration

Because of its short half-life, Dobutamine 12.5 mg/ml concentrate for solution for infusion is administered as a continuous intravenous infusion. After dilution, it should be administered through an intravenous needle or catheter using an IV drip chamber or other suitable metering device to control the rate of flow.

Recommended dosage for adults and the elderly: The usual dose is 2.5 to 10 micrograms/kg/minute. Occasionally, a dose as low as 0.5 micrograms/kg/minute will produce a response.

Rarely, up to 40 micrograms/kg/minute may be required.

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

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

Side-effects, which are dose-related, are infrequent when Dobutamine 12.5 mg/ml concentrate for solution for infusion is administered at rates below 10 micrograms/kg/minute. Rates as high as 40 micrograms/kg/minute have been used occasionally without significant adverse effects.

The final volume administered should be determined by the fluid requirements of the patient. Concentrations as high as 5,000 micrograms/ml have been used in patients on a restricted fluid intake. High concentrations of Dobutamine 12.5 mg/ml concentrate for solution for infusion should only be given with an infusion pump, to ensure accurate dosage.

### ***Cardiac stress testing (Adult population only)***

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

### ***Paediatric population***

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**

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.

### 4.3 Contraindications

- Hypersensitivity to dobutamine, sodium metabisulfite or any of the other ingredients.
- Phaeochromocytoma.
- *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

### 4.4 Special warnings and precautions for use

#### *Adult population*

If an undue increase in heart rate or systolic blood pressure occurs, or if an arrhythmia is precipitated, the dose of dobutamine should be reduced or the drug should be discontinued temporarily.

Dobutamine may precipitate or exacerbate ventricular ectopic activity; rarely has it caused ventricular tachycardia or fibrillation. Because dobutamine facilitates A-V conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

Particular care is required when administering dobutamine to patients with acute myocardial infarction, as any significant increase in heart rate or excessive increases in arterial pressure that occur may intensify ischaemia and cause anginal pain and ST segment elevation.

Inotropic agents, including dobutamine, do not improve haemodynamics in most patients with mechanical obstruction that hinders either ventricular filling or outflow,

or both. Inotropic response may be inadequate in patients with markedly reduced ventricular compliance. Such conditions are present in cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis.

Minimal vasoconstriction has occasionally been observed, most notably in patients recently treated with a  $\beta$ -blocking drug. The inotropic effect of dobutamine stems from stimulation of cardiac  $\beta_1$  receptors and this effect is prevented by  $\beta$ -blocking drugs. However, dobutamine has been shown to counteract the cardiodepressive effects of  $\beta$ -blocking drugs. Conversely, adrenergic blockade may make the  $\beta_1$  and  $\beta_2$  effects apparent, resulting in tachycardia and vasodilatation.

### ***Dobutamine stress echocardiography***

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

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.

The use of Dobutamine 12.5 mg/ml concentrate for solution for infusion as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, bundle branch block, valvular heart disease, aortic outflow obstruction or any cardiac condition that could make them unsuitable for exercise stress testing (see section 4.3)

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

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

- reaching the age-predicted maximal heart rate  $[(220 - \text{age in years}) \times 0.85]$
- systolic blood pressure decrease greater than 20 mmHg
- blood pressure increase above 220/120 mmHg
- progressive symptoms (angina pectoris, dyspnoea, dizziness, ataxia)
- progressive arrhythmia (e.g. coupling, ventricular salvos)
- progressive conduction disturbances
- recently developed wall motility disorders in more than 1 wall segment

(16-segment model)

- increase of 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

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

During the administration of Dobutamine 12.5 mg/ml concentrate for solution for infusion, as with any parenteral catecholamine, heart rate and rhythm, arterial blood pressure and infusion rate should be monitored closely. When initiating therapy, electrocardiographic monitoring is advisable until a stable response is achieved.

Precipitous decreases in blood pressure have occasionally been described in association with dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to base-line values, but rarely intervention may be required and reversibility may not be immediate.

Dobutamine 12.5 mg/ml concentrate for solution for infusion should be used with caution in the presence of severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70 mm Hg).

Hypovolaemia should be corrected when necessary with whole blood or plasma before administering dobutamine.

If arterial blood pressure remains low or decreases progressively during administration of dobutamine despite adequate ventricular filling pressure and cardiac output, consideration may be given to the concomitant use of a peripheral vasoconstrictor agent, such as dopamine or noradrenaline.

Dobutamine 12.5 mg/ml concentrate for solution for infusion contains sodium metabisulfite. Sulfites may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

### ***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.

#### **4.5 Interactions with other medicinal products and other forms of interactions**

##### *Halogenated anaesthetics:*

Although it is less likely than adrenaline to cause ventricular arrhythmias, Dobutamine 12.5 mg/ml concentrate for solution for infusion should be used with great caution during anaesthesia with cyclopropane, halothane and other halogenated anaesthetics.

##### *Entacapone:*

The effects of Dobutamine 12.5 mg/ml concentrate for solution for infusion may be enhanced by entacapone.

##### *Beta-blockers:*

The inotropic effect of dobutamine stems from stimulation of cardiac beta<sub>1</sub> receptors, this effect is reversed by concomitant administration of beta-blockers. Dobutamine has been shown to counteract the effect of beta-blocking drugs. In therapeutic doses, dobutamine has mild alpha<sub>1</sub>- and beta<sub>2</sub>-agonist properties. Concurrent administration of a non-selective beta-blocker such as propranolol can result in elevated blood pressure, due to alpha-mediated vasoconstriction, and reflex bradycardia. Beta-blockers that also have alpha-blocking effects, such as carvedilol, may cause hypotension during concomitant use of dobutamine due to vasodilation caused by beta<sub>2</sub> predominance (see section 4.4 Special warnings and precautions for use).

#### **4.6 Fertility, pregnancy and lactation**

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility, harm to the foetus, or teratogenic effects due to dobutamine. As there are no adequate and well-controlled studies in pregnant women, and as animal reproduction studies are not always predictive of human response, dobutamine should not be used during pregnancy unless the potential benefits outweigh the potential risks to the foetus.

#### **4.7 Effects on ability to drive and use machines**

Not applicable in view of the indications for use and the short half-life of the drug.

#### **4.8 Undesirable effects**

##### *Adult population*

Infusions for up to 72 hours have revealed no adverse effects other than those seen with shorter infusions. There is evidence that partial tolerance develops with continuous infusions of Dobutamine 12.5 mg/ml concentrate for solution for infusion



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

Evaluation of undesirable effects is based on the following frequency scale:

Very common:	$\geq$	1/10
Common:	$\geq$	1/100 to $<$ 1/10
Uncommon:	$\geq$	1/1,000 to $<$ 1/100
Rare:	$\geq$	1/10,000 to $<$ 1/1,000
Very rare:	$<$	1/10,000
Not known		cannot be estimated from the available data

#### Immune system disorders:

Not Known: Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to sulfite sensitivity (see section 4.4 Special warnings and other precautions for use).

#### Blood and lymphatic system disorders

Common: Eosinophilia, inhibition of thrombocyte aggregation (only when continuing infusion over a number of days)

#### Metabolism and nutrition disorders

Very rare: Hypokalaemia

#### Nervous system disorders

Common: Headache

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

#### Cardiac disorders / vascular disorders

Very common: Increase of the heart rate by  $\geq$  30 beats/min

Common: Blood pressure increase of  $\geq$  50 mmHg. Patients suffering from arterial hypertension are more likely to have a higher blood pressure increase.

Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles.

Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised prior to dobutamine infusion.

Vasoconstriction in particular in patients who have previously been treated with beta receptor blockers.

Anginal pain, palpitations

Uncommon: Ventricular tachycardia, ventricular fibrillation

Very rare: Bradycardia, myocardial ischaemia, myocardial infarction, cardiac arrest

Not known: Electrocardiogram ST segment elevation  
Decrease in pulmonary capillary pressure

Eosinophilic myocarditis has been noted in explanted hearts of patients who had undergone treatment with multiple medications including dobutamine or other inotropic agents prior to transplantation.

Children: pronounced increase of heart rate and/or blood pressure as well as a lower decrease of the pulmonary capillary pressure than adults. Increase of pulmonary capillary pressure in children under 1.

Gastrointestinal disorders

Not known: Nausea

Psychiatric disorders

Not known: Restlessness, feeling of heat and anxiety

Renal and urinary disorders

Not known: Urinary urgency

***Dobutamine stress echocardiography***

Cardiac disorders / vascular disorders

Very common: Pectoral anginal discomfort, ventricular extra-systoles with a frequency of > 6/min

Common: Supraventricular extrasystoles, ventricular tachycardia

Uncommon: Ventricular fibrillation, myocardial infarction

Very rare: Occurrence of a second degree atrioventricular block, coronary vasospasms.

Hypertensive/hypotensive blood pressure decompensation, occurrence of an intracavitary pressure gradient, palpitations

Not known: Stress cardiomyopathy (Takotsubo syndrome) (see section 4.4)  
Left ventricular outflow tract obstruction  
Fatal cardiac rupture

Respiratory system, thoracic and mediastinal disorders

Common: Bronchospasm, shortness of breath

Gastrointestinal disorders

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Exanthema

Very rare: Petechial bleeding

Musculoskeletal and connective tissue disorders

Common: Chest pain

Renal and urinary disorders

Common: Increased urgency at high dosages of infusion

#### General disorders and administration site conditions

Common: Fever, phlebitis at the injection site  
In case of accidental paravenous infiltration, local inflammation may develop.

Very rare: Cutaneous necrosis

#### ***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.

#### 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 – Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

### **4.9 Overdose**

Overdoses of Dobutamine 12.5 mg/ml concentrate for solution for infusion have been reported rarely. The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath and anginal and non-specific chest pain. The positive inotropic and chronotropic effects of dobutamine may cause hypertension, tachyarrhythmias, myocardial ischaemia and ventricular fibrillation. Hypotension may result from vasodilatation.

The duration of action of Dobutamine 12.5 mg/ml concentrate for solution for infusion is generally short (half-life, approximately 2 minutes). Dobutamine 12.5 mg/ml concentrate for solution for infusion should be temporarily discontinued until the patient's condition stabilises. The patient should be monitored and any appropriate resuscitative measures initiated promptly.

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

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

#### ***Adult population***

Dobutamine directly stimulates  $\beta$ -adrenergic receptors and is generally considered a selective  $\beta_1$ -adrenergic agonist, but the mechanisms of action of the drug are complex. It is believed that the  $\beta$ -adrenergic effects result from stimulation of adenylyl cyclase activity. In therapeutic doses, dobutamine also has mild  $\beta_2$  - and  $\alpha_1$  - adrenergic receptor agonist effects, which are relatively balanced and result in minimal net direct effect on systemic vasculature. Unlike dopamine, dobutamine does not cause release of endogenous norepinephrine. The main effect of therapeutic doses of dobutamine is cardiac stimulation. While the positive inotropic effect of the drug on the myocardium appears to be mediated principally via  $\beta_1$ -adrenergic stimulation, experimental evidence suggests that

$\alpha_1$ -adrenergic stimulation may also be involved and that the  $\alpha_1$ -adrenergic activity results mainly from the (-) -stereoisomer of the drug.

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

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

### ***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.

## **5.2 Pharmacokinetic properties**

### ***Adult population***

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

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

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

### ***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**

No further information other than that which is included in the Summary of Products Characteristics.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium Metabisulfite BP  
Sodium Hydroxide EP  
Hydrochloric Acid EP  
Water for Injections EP  
Carbon Dioxide HSE

## **6.2 Incompatibilities**

Do not add Dobutamine 12.5 mg/ml concentrate for solution for infusion to 5% Sodium Bicarbonate intravenous infusion BP or to any other strongly alkaline solutions. Because of potential physical incompatibilities, it is recommended that dobutamine hydrochloride not be mixed with other drugs in the same solution.

Dobutamine 12.5 mg/ml concentrate for solution for infusion should not be used with other agents or diluents containing both sodium metabisulfite and ethanol.

## **6.3 Shelf life**

36 months.

## **6.4 Special precautions for storage**

Protect from light, do not store above 25°C.

## **6.5 Nature and contents of container**

20 ml clear glass ampoule. Packed in cardboard cartons to contain 1, 5 or 10 ampoules x 20 ml.

## **6.6 Special precautions for disposal**

No special requirements

## **7. MARKETING AUTHORISATION HOLDER**

hameln pharma ltd  
Nexus, Gloucester Business Park  
Gloucester, GL3 4AG  
UK

## **8. MARKETING AUTHORISATION NUMBER**

PL 01502/0054

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

16<sup>th</sup> December 1994

## **10. DATE OF REVISION OF THE TEXT**

16/02/2022