Public Assessment Report

Decentralised Procedure

Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion

Procedure No: UK/H/3913/001/DC

UK Licence No: PL 20568/0037

Claris Lifesciences UK Limited
LAY SUMMARY

On 28 April 2011, Austria, Belgium, Germany, Estonia, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Portugal, Romania and the UK agreed to grant a Marketing Authorisation to Claris Lifesciences UK Limited for the medicinal product Dobutamine 12.5 mg/ml Concentrate for solution for infusion (PL 20568/0037; UK/H/3913/001/DC). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 17 May 2011. This is a prescription-only medicine (POM) used to stimulate the heart in adults who have heart failure caused by a heart attack, open-heart surgery and heart disease. Dobutamine 12.5 mg/ml Concentrate for solution for infusion is also used for testing the heart when exercise testing is not possible.

Dobutamine 12.5 mg/ml Concentrate for solution for infusion contains the active ingredient dobutamine hydrochloride, which belongs to a group of medicines called beta-receptor agonists (heart stimulants).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Dobutamine 12.5 mg/ml Concentrate for solution for infusion outweigh the risks; therefore, a Marketing Authorisation has been granted.
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## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Dobutamine 12.5 mg/ml Concentrate for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Dobutamine hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Concentrate for solution for infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>12.5 mg/ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Claris Lifesciences UK Limited</td>
</tr>
<tr>
<td></td>
<td>Golden Gate Lodge</td>
</tr>
<tr>
<td></td>
<td>Crewe Hall, Weston Road</td>
</tr>
<tr>
<td></td>
<td>Crewe, Cheshire CW1 6UL</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Austria, Belgium, Germany, Estonia, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Portugal and Romania</td>
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<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/3913/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 28 April 2011</td>
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</tbody>
</table>
Module 2
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 1 ml contains 12.5 mg of dobutamine (as 14.01 mg dobutamine hydrochloride).
Each 20 ml ampoule contains 250 mg of dobutamine (as 280.2 mg dobutamine hydrochloride).
Each 1 ml contains 0.15 mg of Sodium metabisulphite.
Each 20 ml contains 3.0 mg of Sodium metabisulphite.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion
Clear, colourless or slightly yellow solution.
pH between 2.50 and 4.00

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Dobutamine is indicated for adults who require positive inotropic support in the treatment of low
output cardiac failure normally associated with myocardial infarction, open-heart surgery,
cardiomyopathies, septic shock and cardiogenic shock.
Dobutamine can also be used for cardiac stress testing, in cases when exercise stress testing is not
feasible.

4.2 Posology and method of administration
Method of administration
Dobutamine Concentrate should be diluted before use and administered by IV infusion only.
The concentration of the dobutamine administered depends upon the dosage and fluid requirements of
the individual patient. The final concentrations generally used for perfusion are 250 micrograms/ml,
500 micrograms/ml or 1000 micrograms/ml. For special precautions for storage of the prepared
diluted infusion see section 6.4. High concentrations of dobutamine should only be given with an
infusion pump or other suitable apparatus to ensure accurate dosage. Due to its short half-life
dobutamine should be administered as a continuous intravenous infusion. Dobutamine should be
administered intravenously through an intravenous needle or catheter. The following sterile solutions
for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate
solution.

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

Dosage for Infusion delivery systems:
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) with any of the approved diluents (see section 6.6).

<table>
<thead>
<tr>
<th>Dosage range</th>
<th>Specifications in ml/h* (drops/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 kg</td>
</tr>
<tr>
<td>Low 2.5 µg/kg/min</td>
<td>ml/h (drops/min)</td>
</tr>
<tr>
<td>Medium 5 µg/kg/min</td>
<td>ml/h (drops/min)</td>
</tr>
<tr>
<td>High 10 µg/kg/min</td>
<td>ml/h (drops/min)</td>
</tr>
</tbody>
</table>
* For double concentration, i.e. 500 mg Dobutamine added to 500 ml, or 250 mg added to 250 ml solution, infusion rates must be halved.

The dose to be administered can be calculated taking into account the table below. Infusion rates in millilitres/min can be obtained by multiplying infusion rates for each concentration (ml/kg/min) by patient’s weight (kg).

<table>
<thead>
<tr>
<th>Dose micrograms/kg/min</th>
<th>Infusion rate ml/kg/min</th>
<th>Infusion rate ml/kg/min</th>
<th>Infusion rate ml/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>0.01</td>
<td>0.005</td>
<td>0.0025</td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>7.5</td>
<td>0.03</td>
<td>0.015</td>
<td>0.0075</td>
</tr>
<tr>
<td>10</td>
<td>0.04</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>12.5</td>
<td>0.05</td>
<td>0.025</td>
<td>0.0125</td>
</tr>
<tr>
<td>15</td>
<td>0.06</td>
<td>0.03</td>
<td>0.015</td>
</tr>
</tbody>
</table>

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) with any of the approved diluents (see section 6.6).

<table>
<thead>
<tr>
<th>Dosage range</th>
<th>Specifications in ml/h (ml/min)</th>
<th>Patient’s weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 2.5 µg/kg/min</td>
<td>ml/h (ml/min)</td>
<td>1.5 (0.025)</td>
</tr>
<tr>
<td>Medium 5 µg/kg/min</td>
<td>ml/h (ml/min)</td>
<td>3.0 (0.05)</td>
</tr>
<tr>
<td>High 10 µg/kg/min</td>
<td>ml/h (ml/min)</td>
<td>6.0 (0.10)</td>
</tr>
</tbody>
</table>

Posology
Adults:
Inotropic support of the myocardium:
The usual dose is 2.5 to 10 micrograms/kg/min, which should be adjusted according to the patient’s heart rate, blood pressure, cardiac output and urine output. The infusion must be started at a rate of 2.5 micrograms/kg/min and the dose may be increased in intervals of 10-30 minutes until desired hemodynamic response is achieved or until side effects, such as excessive tachycardia, arrhythmia, headache or tremor limit a further increase in dosage. The dose should be adjusted individually according to heart rate and rhythm, blood pressure and urinary flow. Occasionally, a dose as low as 0.5 micrograms/kg/min will elicit a response. Up to 40 micrograms/kg/min may occasionally be required, but this is rare.

During prolonged continuous infusion (48-72 hours), a decrease in haemodynamic response may occur, which makes an increase in dose necessary.

Dosage for cardiac stress testing:
The use of dobutamine in cardiac stress testing 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 including the availability of a defibrillator and personnel specially trained in resuscitation are present.

The recommended dosage is an incremental increase in infusion rates from 5 micrograms/kg/minute to 10, 20, 30 and a maximum of 40 micrograms/kg/minute, each dose being infused for 3 minutes. In addition atropine can be added during further infusion of the peak dose. Continuous electrocardiogram (ECG) monitoring is required and the infusion may be terminated in the event of ST-segment
depression of > 0.2 mV (2 mm) measured 80 ms after the J point, a ST-segment elevate of > 0.1 mV (1 mm) in patients without history of myocardial infarction, or any significant cardiac arrhythmias. The infusion of dobutamine should be terminated if the heart rate reaches 85% of the age-predicted maximum, systolic blood pressure rises above 220 mmHg or a symptomatic decrease in systolic blood pressure > 40 mmHg from baseline, new cardiac wall motion abnormalities, severe chest pain or any non-tolerable adverse effect occurs.

Elderly:
No variation in dosage is suggested. Close monitoring is required for blood pressure, urine flow and peripheral tissue perfusion.

Cardiac stress testing: When used as an alternative to exercise for cardiac stress testing the recommended dose should start at 5 micrograms/kg/minute, and the dose should be increased incrementally by 5 micrograms/kg/minute every 8 minutes, to a maximum rate of 20 micrograms/kg/minute. 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 Patients
Doses of 1 to 15 µg dobutamine/kg/min have been administered. 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 µg dobutamine/kg/min.

The required dose for children should be titrated in order to allow for the supposedly smaller “therapeutic width” in children. An initial dose of 0.5 micrograms/kg/minute is recommended, which is increased every 10-30 minutes until reaching the desired response.

4.3 Contraindications
Patients with known or suspected hypersensitivity to dobutamine, sodium metabisulphite or other sulphates or to any of the other excipients.

Patients with marked mechanical obstruction affecting ventricular filling or outflow, or both, such as cardiac tamponade, severe valvular aortic stenosis, constrictive pericarditis, hypertrophic obstructive cardiomyopathy or idiopathic hypertrophic subaortic stenosis.

Patients with hypovolaemia unless it has been corrected by volume replacement.

Uncontrolled serious ventricular arrhythmias.

In addition, for cardiac stress test: Recent myocardial infarction (within 30 days), aortic dissection, aortic aneurysm, unstable angina, uncontrolled hypertension, uncontrolled arrhythmias (including uncontrolled atrial fibrillation), known severe ventricular arrhythmias, electrolyte imbalance and severe anaemia.

Phaeochromocytoma

4.4 Special warnings and precautions for use
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. Dobutamine increases atrioventricular conduction, patients with atrial flutter or fibrillation may develop rapid ventricular responses.

There is a possibility that dobutamine can cause a significant increase in heart rate or excessive increase in arterial pressure which may intensify or extend myocardial ischaemia, cause anginal pain and ST segment elevation, therefore care should be exercised following myocardial infarction (see section 4.3).
Dobutamine will not improve haemodynamics in most patients with mechanical obstruction affecting ventricular filling or outflow, or both (see section 4.3).

Inotropic response may be inadequate in patients with markedly reduced ventricular compliance, e.g. with cardiac tamponade, valvular aortic stenosis, and idiopathic hypertrophic subaortic stenosis (see section 4.3). Via competitive receptor inhibition, the catecholaminergic effect of dobutamine can be reduced with simultaneous administration of a beta receptor blocker. In addition, the alpha effects predominant at that time may cause a peripheral vasoconstriction with a consequent increase of blood pressure.

Administration
Before administration of dobutamine, hypovolaemia should be corrected with an appropriate plasma volume expander (see section 4.3). Like other drugs with beta2-agonist activity, dobutamine may produce slight reductions in serum potassium concentrations and hypokalaemia may occur occasionally. Consideration should be given to monitoring serum potassium during dobutamine therapy.

During administration of dobutamine, heart rate and rhythm, arterial blood pressure, and infusion rate should be monitored closely. When starting therapy, electrocardiographic monitoring is recommended until a stable response is obtained.

Caution
Dobutamine should be used with caution in severe hypotension complicating cardiogenic shock (mean arterial pressure less than 70 mm Hg). If the blood pressure drops quickly, decreasing the dose or stopping the infusion typically results in a return to base-line blood pressure values. Occasionally intervention may be required and reversibility may not be immediate.

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 use of a peripheral vasoconstrictor agent e.g. noradrenaline or dopamine.

Dobutamine Concentrate for solution for infusion contains sodium metabisulphite in the formulation. This may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulphite sensitivity in the general population is unknown but is probably low; such sensitivity seems to occur more frequently in asthmatic patients (see section 4.3).

Dobutamine should only be used under the direct supervision of physicians to whom facilities for regular, intensive monitoring of cardiovascular and renal parameters, in particular, blood volume, myocardial contractility, electrocardiography, urine flow rate, and blood and pulse pressure and, if possible, cardiac output and pulmonary wedge pressure (PWP) are available.

After cessation of a longterm therapy (more than 7 days) with dobutamine a decrease in cardiac output and an increase in PWP was observed.

In patients with pre-existing hypertonia an increase in blood pressure could occur.

Since the effect of dobutamine on impaired renal and hepatic function is not known, close monitoring is advisable.

Intravenous continuous dobutamine is of limited benefit and may in fact be harmful to patients with advanced heart failure, with respect to quality of life and survival rates.

Dobutamine may alter insulin and glucose plasma levels. Consequently, in diabetic patients, the glucose concentration should be controlled and the insulin dose adjusted if necessary.

The use of dobutamine as an alternative to exercise for cardiac stress testing is not recommended for patients with unstable angina, bundle branch block or any cardiac condition that could make them unsuitable for exercise stress testing.

As with other catecholamines, dobutamine may trigger an onset of angina in patients with ischaemic heart disease and consequently particular care should be exercised when dobutamine is administered to patients with ischaemic heart disease.
Particular caution has to be exercised when using dobutamine in patients treated with monoamine oxidase inhibitors (MAOs) and in patients with pheochromocytoma or with hyperthyroidism due to the increased catecholamine levels or sensitivity, which could result in marked increases in blood pressure, heart rate and higher incidence of arrhythmias.

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 dyskinetic and thinned inferior wall. Patients considered at risk of cardiac rupture during dobutamine testing should therefore be carefully evaluated prior to testing.

Dobutamine stress echocardiography
Because of possible life-threatening complications the use within the scope of ischemia and vitality diagnostics is only allowed by a physician with sufficient personal experience in stress echocardiography.

Dobutamine stress echocardiography within the scope of ischemia and vitality diagnostics 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 >20 mmHg,
- blood pressure increase to >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 > 1 wall segment (16-segment model),
- increase of endystolic volume,
- development of repolarisation abnormality (due to ischemia horizontal or down sloping ST segment depression >0.2 mV at an interval of 80 (60) ms after the J point compared to baseline, progressive or monophasic ST segment elevation >0.1 mV in patients without a previous myocardial infarction,
- reaching peak dose.

Also in case of serious complications (see section 4.8) a Dobutamine stress echocardiography has to be immediately disrupted.

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

This medicinal product contains 0.0504 mmol (1.160 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-adrenergic blocking agents
In animals the cardiac effects of dobutamine are antagonised by beta-adrenergic blocking agents such as propranolol and metoprolol, resulting in predominance of alpha-adrenergic blocking agents and increased peripheral resistance.

Conversely, alpha-adrenergic blockade may make the beta₁ and beta₂ effects apparent, resulting in tachycardia and vasodilatation.

The addition of dipyridamole to dobutamine for echocardiography can cause potentially hazardous hypotension. The combination should not be used in patients suspected of coronary heart disease.

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

When adding atropine at the highest titration level of Dobutamine, the following can be observed:
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.

**General anaesthetics**

Ventricular arrhythmias have been reported in animals receiving usual doses of dobutamine during halothane or cyclopropane anaesthesia; therefore, caution should be exercised when administering dobutamine to patients receiving these anaesthetics.

Concomitant use of dobutamine and MAOIs may result in marked increases in blood pressure and heart rate and in increased incidence of arrhythmias. Even life-threatening events such as hypertensive crisis, cardiovascular collapse, intracranial haemorrhage and arrhythmias may result.

Pre-treatment or concomitant administration of β-receptor blocking drugs may result in decrease in inotropic and chronotropic effects due to competitive binding to the β-receptor and in predominance of the α1-mediated effects resulting in peripheral vasodilatation.

Peripheral vasodilators (e.g. nitrates, sodium nitroprusside) in combination with dobutamine may increase cardiac output and decrease systemic peripheral resistance and ventricular filling pressure more than either drug alone.

Concomitant use theophylline with dobutamine resulted in an increase in the heart rate, in one clinical study.

Concurrent use of dobutamine and dopamine increases systemic arterial pressure markedly and prevents the increase in ventricular filling pressure seen with dopamine alone.

Concomitant use of dobutamine and peripheral vasoconstrictor agents such as noradrenaline increases systemic arterial blood pressure more markedly, than either drug alone.

Concomitant administration of dobutamine and ACE-inhibitors (e.g. captopril) may result in an increase in cardiac output accompanied by increased myocardial oxygen consumption. The occurrence of chest pain and arrhythmias has been reported with this combination.

The effects of dobutamine may be enhanced by the concomitant use with entacapone. The hypertensive effects of dobutamine may be antagonised by antipsychotics.

There is an increased risk of hypertension when dobutamine is given with doxapram.

There is an increased risk of ergotism when dobutamine is given with ergotamine and methysergide.

Concomitant use of dobutamine and oxytocin may cause hypertension (due to the enhanced vasopressor effects).

Addition of atropine sulphate enhances the increases in heart rate induced by dobutamine and may counteract the deceleration in heart rate occasionally observed in dobutamine cardiac stress testing.

### 4.6 Pregnancy and lactation

**Pregnancy**

There are no adequate data on the safety of dobutamine in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition and post-natal development, but it is not known whether dobutamine crosses the placenta (see section 5.3). The potential risk for humans is unknown. Dobutamine should not be used during pregnancy unless the potential benefits to the woman outweigh the potential risks to the fetus.

**Lactation**

It is not known whether dobutamine is excreted in animal or human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with dobutamine should be made taking into account the benefit of breast-feeding to the child and the benefit of dobutamine therapy to the woman.
4.7 Effects on ability to drive and use machines
Not relevant in view of the indications for use and the short half-life of dobutamine.

4.8 Undesirable effects
Infusions for up to 72 hours have revealed no adverse effects other than those seen with shorter infusions. There is evidence that partial tolerance develops with continuous infusions of Dobutamine Concentrate for 72 hours or more; therefore, higher doses may be required to maintain the same effects.

The following terminologies have been used in order to classify the occurrence of undesirable effects:

<table>
<thead>
<tr>
<th>Frequency Grouping</th>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>(≥ 1/10)</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>(≥ 1/100 to &lt; 1/10)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>(≥ 1/1000 to &lt; 1/100)</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>(≥ 1/10000 to &lt; 1/1000)</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>(&lt; 1/10000)</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>(cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders:
Common: Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported.
Rare: Sodium metabisulphite may cause allergic type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes (see section 4.4).

Metabolism and nutrition disorders:
Very rare: As with other catecholamines, decreases in serum potassium concentrations have occurred. Consideration should be given to monitoring serum potassium.

Nervous system disorders:
Common: Headache
Very rare: Myoclonus has been reported in patients with severe renal failure receiving dobutamine.

Cardiac disorders:
Very common: Increased heart rate, palpitations, severe chest pain, irregular heartbeats, arrhythmia, ventricular tachycardia, coronary artery spasm, electrocardiogram ST segment elevation.

Uncommon: Atrial fibrillation, ventricular fibrillation, left ventricular outflow tract obstruction.

Very rare: myocardial ischaemia, myocardial infarction, eosinophilic myocarditis, fatal cardiac rupture during dobutamine stress testing (see section 4.4).

Vascular disorders:
Common: Hypertension. Marked increase in systolic blood pressure indicates overdose (see also section 4.5).
Uncommon: Hypotension (see sections 4.4 & 4.5). Slight vasoconstriction, especially in patients with pre-treated with β-blockers.

Respiratory, thoracic and mediastinal disorders:
Common: Shortness of breath, bronchospasm, asthma (see Immune system disorders).

Gastrointestinal disorders:
Common: Nausea.

Renal and urinary disorder:
Not known: urinary urgency

General disorders and administration site conditions:
Common: Non-specific chest pain.
Rare: Phlebitis has occasionally been reported and local inflammatory changes have been described following inadvertent infiltration.
Very rare: Cutaneous necrosis

4.9 Overdose
Overdose has been rarely reported.

Symptoms
The symptoms of toxicity may include anorexia, nausea, vomiting, tremor, anxiety, palpitations, headache, shortness of breath, fatigue 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 vasodilation. The duration of action of dobutamine is generally short (half-life, approximately 2 minutes).

Treatment
Due to the short duration of action of dobutamine, usually only a reduction in infusion rate or a transient cessation of infusion is necessary until stabilisation of the patient.

Temporarily discontinue dobutamine until the patient's condition stabilises. The patient should be monitored and any appropriate resuscitative measures started immediately.

Forced diuresis, peritoneal dialyses, 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
Pharmacotherapeutic group: cardiac stimulants excluding cardiac glycosides, adrenergic and dopaminergic agents

ATC code: C01CA07
Dobutamine is a selective beta-adrenergic agonist whose mechanism of action is complex.

It is believed that the beta-adrenergic effects result from stimulation of adenyl cyclase activity. In therapeutic doses, dobutamine also has mild beta2 and alpha1 adrenergic receptor agonist effects, which are relatively balanced and result in minimal net direct effect on systemic vasculature. 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 beta1-adrenergic stimulation, experimental evidence suggests that alpha1-adrenergic stimulation may also be involved and that the alpha1-adrenergic activity results mainly from the (-)-stereoisomer of the drug.

The beta1-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. 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.

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

Absorption: Orally administered dobutamine is rapidly metabolised in the 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. Studies on the mutagenic or carcinogenic potential of dobutamine have not been conducted. Studies in rats and rabbits revealed no evidence of fetal harm or teratogenic effect. No influence on fertility was seen in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulphite (E223)
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for Injections

6.2 Incompatibilities

Dobutamine Concentrate has been reported to be incompatible with alkaline solutions and should not be mixed with sodium bicarbonate 5%, or other strong alkaline solutions i.e. aminophylline, furosemide. Precipitation has occurred with bumetanide, calcium gluconate, insulin, diazepam and phenytoin. Because of the potential physical incompatibilities, Dobutamine Concentrate should not be mixed with other drugs in the same solution.

Dobutamine should not be used with drugs or diluents containing bisulphites or ethanol. This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°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 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Prior to first use, do not store above 25°C.

Infusions must be aseptically prepared.

For storage conditions of the diluted medicinal product, see section 6.3.

Discard any unused product.

6.5 Nature and contents of container

20 ml clear glass ampoule (type I) with a pack size of 5 and 1 ampoules.

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
Dobutamine Concentrate should be diluted before use and administered by IV infusion only.

The final concentrations generally used for perfusion are 250 micrograms/ml, 500 micrograms/ml or 1000 micrograms/ml. See section 4.2 for method and duration of administration.

The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate solution.

Solutions of dobutamine hydrochloride may have a pink discolouration. This discolouration, which will increase with time, results from a slight oxidation of the drug. However, there is no significant loss of drug potency within the recommended maximum in-use storage time of 24 hours at 2°C - 8°C.

Any unused product or waste material should be disposed of in accordance with local requirements.
Dobutamine 12.5 mg/ml Concentrate for solution for infusion

Dobutamine 12.5 mg/ml Concentrate for solution for infusion

doobutamine

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

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What Dobutamine is and what it is used for
2. Before you are given Dobutamine
3. How you will be given Dobutamine
4. Possible side effects
5. How to store Dobutamine
6. Further information

1. What Dobutamine is and what it is used for

Dobutamine contains the active ingredient dobutamine, which belongs to a group of medicines called beta-receptor agonists (heart stimulants). Dobutamine is used to stimulate the heart in adults who have heart failure caused by heart attack, open heart surgery and heart disease. Dobutamine can also be used to treat chest pain when exercise testing is not possible.

2. Before you are given Dobutamine

You should not be given Dobutamine if:
- You are allergic (hypersensitive) or might be allergic to dobutamine, sodium metabisulphite, sulphites, or any of the other ingredients of Dobutamine (see list of ingredients in section 6). An allergic reaction may include rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue.
- You have a low blood volume that has not been corrected (your doctor will tell you this).
- You have an obstruction that interferes with blood flow out of your heart (your doctor will tell you this).
- You have uncontrolled arrhythmia (heart rhythm)
- You suffer from high blood pressure due to a tumour near the kidney (Phaeochromocytoma).

You will also not be given Dobutamine to test your heart if:
- You have unstable (uncontrolled) angina
- You have an electrolyte (salt) imbalance
- You have suffered a heart attack within the last 30 days
- You have suffered an acute encephalapax (a weakness on one side of the body)
- You have a low blood pressure (your doctor will tell you this).
- You have uncontrolled high blood pressure
- You have severe anaemia (low red blood cells)
- You have suffered an acute encephalapax (a bleeding caused by a tear in the wall of the aorta, the major blood vessel that feeds blood to the body).

Take special care with Dobutamine and tell your doctor if you have any of the following conditions:
- Any heart disorder
- Hypothyroidism (low thyroid hormone)
- A tumour of the adrenal gland
- A condition in which the concentration of potassium in the blood is low (Reduction in serum potassium concentration and hypokalaemia)
- A liver or kidney disorder
- Severe hypertension (high blood pressure)
- Asthma
- Diabetes mellitus
- Hypervolaemia (high blood pressure)

Taking other medicines

You should tell your doctor if you are taking or have taken any of the following medicines as they may interact with your Dobutamine:
- Monoamine oxidase inhibitors (treatments for depression)
- Beta-adrenergic blockers such as propranolol or metoprolol
- Alpha-adrenergic blockers (for high blood pressure or enlarged prostate gland)
- ACE-inhibitors, e.g. captopril (for high blood pressure or heart failure)
- Antipsychotics (treatments for mental illness)
- Dipyridamole (used in labour)
- Peripheral vasodilator agents such as noradrenaline
- Peripheral vasoconstrictor agents such as nitrates, sodium nitroprusside

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

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

Pregnancy and lactation

You will not be given Dobutamine if you are pregnant or breast-feeding unless your doctor thinks it is necessary.

Driving and using machines

Dobutamine has no effect on your ability to drive or use machinery.

Important information about some of the ingredients of Dobutamine

This medicinal product contains less than 1 millimole (23 mg) of sodium; i.e. essentially sodium-free.

This medicinal product contains sodium metabisulphite, which may rarely cause severe hypersensitivity reactions and bronchospasm.

3. How you will be given Dobutamine

You will be given Dobutamine in hospital by a doctor or nurse. Dobutamine is diluted and infused into a vein.

Dosage for stimulation of the heart

Adults and the elderly:
The usual dose is 2.5 to 10 micrograms/kg body weight/min, which is adjusted according to the heart rate, blood pressure, heart output and urine output. Doses of 40 micrograms/kg/min may occasionally be required.

Dosage for stress testing of the heart

Adults:
The recommended dosage is an incremental increase from 5 to maximum 40 micrograms/kg/min. In conjunction with exercise in the exercise laboratory.

Elderly:
The recommended dosage is an incremental increase from 5 to maximum 20 micrograms/kg/min. In conjunction with exercise in the exercise laboratory.

Doses of 1 to 15 micrograms/kg/min have been administrated. The required dose for children should be titrated in order to allow for the supposedly smaller "therapeutic width" in children. An initial dose of 0.5 micrograms/kg/min is recommended, which is increased every 10-30 minutes until reaching the desired response.

If you are given more Dobutamine than you should

Your infusion will be stopped and you will be monitored closely. Your doctor will know the correct amount to give you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

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

- Increased heart rate
- Severe chest pain
- Arrhythmia (too fast or too slow heart beat)
- Electrocardiogram ST segment elevation
- Coronary artery spasm (tendency, sudden contraction in one location of heart muscles)

- Palpitations
- Irregular heartbeats
- Ventricular tachycardia (fast heart rhythm that originates in one of the ventricles of the heart)
Dobutamine 12.5 mg/ml Concentrate for solution for infusion

UK/H/3913/001/DC

Common (affects 1 to 10 users in 100)
- Hypersensitivity reactions including rash
- Eosinophilia (high concentration of eosinophils granules cells in blood)
- Hypertension
- Marked increase in systolic blood pressure indicates overdose
- Shortness of breath
- Nausea

Uncommon (affects 1 to 10 users in 1,000)
- Atrial fibrillation (abnormal heart rhythm involves the two upper chambers/atria)
- Ventricular fibrillation (uncoordinated contraction of the cardiac muscle of the ventricles)

Rare (affects 1 to 10 users in 10,000)
- Phlebitis (formation of blood clots)
- Anaphylactic reactions (severe hypersensitivity allergic reaction)

Very rare (affects less than 1 user in 10,000)
- As with other catecholamines, decreases in serum potassium concentrations have occurred.
- Myocardial ischemia (reduced blood supply to the heart muscle)
- Myocardial infarction (heart attack)
- Eosinophilic myocarditis (inflammation of the heart muscle)
- Fatal cardiac rupture during dobutamine stress testing.

Local inflammatory changes
- Severe life-threatening asthma episodes may be due to substrate sensitivity
- Local inflammatory changes
- Severe life-threatening asthma episodes may be due to substrate sensitivity
- Local inflammatory changes
- Severe life-threatening asthma episodes may be due to substrate sensitivity
- Local inflammatory changes
- Severe life-threatening asthma episodes may be due to substrate sensitivity

Unknown (cannot be estimated from the available data)
- Urinary urgency

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to use Dobutamine

Keep out of the reach and sight of children.

Do not use Dobutamine after the expiry date which is stated on the visi and the outer c outer after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25°C. Discard any unused product.

Dobutamine Concentrate should be diluted for use and administered by IV infusion only. The final concentrations generally used for perfusion are 250 micrograms/ml, 500 micrograms/ml or 1000 micrograms/ml.

The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate solution.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C-8°C unless reconstitution (infusion) etc. has taken place in a controlled and validated aseptic conditions.

Diluted solutions of dobutamine hydrochloride may have a slight discoloration. This discoloration, which will increase with time, results from a slight oxidation of the drug. However, there is no significant loss of drug potency within the recommended maximum in use storage time of 24 hours at 2°C-8°C.

Do not use Dobutamine if you notice visible signs of deterioration or visible particles in the product.

Your doctor or pharmacist is responsible for the correct storage, use and disposal of Dobutamine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Dobutamine contains:
- The active substance is dobutamine.
- Each 1 ml contains 12.5 mg of dobutamine (as 14.01 mg dobutamine hydrochloride).
- Each 20 ml ampoule contains 250 mg of dobutamine (as 280.2 mg dobutamine hydrochloride).

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and should be used within 24 hours at 2°C-8°C unless reconstitution (infusion) etc. has taken place in a controlled and validated aseptic conditions.

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Do not use Dobutamine if you notice visible signs of deterioration or visible particles in the products.

Your doctor or pharmacist is responsible for the correct storage, use and disposal of Dobutamine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Marketing Authorisation
- Holder: Claris Lifesciences (UK) Limited
- Manufacturer: Peckforton Pharmaceuticals Limited
- Crewe Hall, Golden Gate Lodge, Crewe, Cheshire, CW1 6UL
- Crewe Hall, Golden Gate Lodge, Crewe, Cheshire, CW1 6UL

This medicinal product is authorised in the Member States of the EEA under the following names:
- Austria: Dobutamin (Crisis 12.5 mg/ml Concentrate zur Herstellung einer Infusionslösung)
- Belgium: Dobutamin Crisis 12.5 mg/ml Concentrate voor Influsie
- Germany: Dobutamin Crisis 12.5 mg/ml Konzentrat zur Herstellung einer Infusionslösung
- Estonia: Dobutamine Crisis
- France: Dobutamine Clairs 12.5 mg/ml Concentrate for Solution for Infusion
- Ireland: Dobutamine Clairs 12.5 mg/ml Concentrate for Solution for Infusion
- Italy: Dobutamine Clairs 12.5 mg/ml Concentrate for Solution for Infusion
- Latvia: Dobutamine Clairs 12.5 mg/ml koncentrāts infuziju āķītai āķītas pārdošanai
- Lithuania: Dobutamine Clairs 12.5 mg/ml koncentrāts infuzijai iršainai
- Luxembourg: Dobutamine Clairs 12.5 mg/ml Concentrate for Solution for Infusion
- The Netherlands: Dobutamine Clairs 12.5 mg/ml Concentraat voor oplossing voor infusie
- Portugal: Dobutamine Clairs 12.5 mg/ml Concentrado para solução perfusível
- Romania: Dobutamin Clairs 12.5 mg/ml concentrat pentru soluție perfuzibilă
- UK: Dobutamine 12.5 mg/ml Concentrate for Solution for Infusion

This leaflet was last approved in 04/2011

The following information is intended for medical or healthcare professionals only

Dobutamine Concentrate should be diluted before use and administered by IV infusion only through an intravenous needle or catheter. Due to its short half-life dobutamine should be administered as a continuous intravenous infusion. High concentrations of dobutamine should only be given with an infusion pump to ensure accurate dosage or other suitable apparatus.

The following sterile solutions for IV infusion may be used for the dilution of dobutamine before use: sodium chloride solution 0.9% (9 mg/ml), glucose solution 5% (50 mg/ml), dextrose solution 5% (50 mg/ml), or Ringer lactate solution.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage conditions prior to use is the responsibility of the user and should not be longer than 24 hours at 2°C-8°C unless reconstitution (infusion) etc. has taken place in a controlled and validated aseptic conditions.

Any unused product or wastepaper should be disposed of in accordance with local requirements.

1400052509
Module 4

Ampoule label:

Each 1 ml contains 12.5 mg of dobutamine (as 14.0 mg dobutamine hydrochloride).
Each 20 ml ampoule contains 250 mg of dobutamine (as 290.2 mg dobutamine hydrochloride).
Excipients: Sodium metabisulphite (E223), Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment). Water for Injections
See leaflet for further information.

Storage: Do not store above 25°C. For in use storage conditions, refer to package leaflet information.

Code No.: CUWDRUG(1165)
M.A. No.: RL.2056/91/0037
PA1052/01/2001

Batch:
Mfg:
EXP:

Cartons:
Each 1 ml contains 12.5 mg of dobutamine (as 14.01 mg dobutamine hydrochloride).
Each 20 ml ampoule contains 250 mg of dobutamine (as 280.2 mg dobutamine hydrochloride).

Excipients: Sodium metabisulphite (E223), Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment), Water for Injections.

See leaflet for further information.

Concentrate for solution for infusion
5 x 20 ml ampoules.

Storage: Do not store above 25°C. For in use storage conditions, refer to package leaflet before use.

Single use only. Discard any unused contents.
Keep out of the reach and sight of children.

Marketing Authorisation Holder:
Claris Lifesciences UK Limited
Crew Hill, Crewe, Cheshire, CW1 8UL, United Kingdom.

Dobutamine 12.5 mg/ml
Concentrate for solution for infusion
Dobutamine

For Intravenous use
Must be diluted
Read the package leaflet before use

Claris

Dobutamine 12.5 mg/ml
Concentrate for solution for infusion
Dobutamine
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Dobutamine 12.5 mg/ml Concentrate for solution for infusion (PL 20568/0037; UK/H/3913/001/DC) could be approved. The product is a prescription-only medicine indicated in adults who require positive inotropic support for the treatment of low output cardiac failure normally 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 be used for cardiac stress testing, in cases when exercise stress testing is not feasible.

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Estonia, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Portugal and Romania as Concerned Member States (CMS). The application was submitted under Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Dobutrex Injection 12.5 mg/ml (Eli Lilly & Company Limited, UK), which was first approved in the UK on 10 October 1978.

The active ingredient dobutamine hydrochloride is a direct-acting inotropic agent whose primary activity results from stimulation of the beta receptors of the heart while producing mild chronotropic, hypertensive, arrhythmogenic, and vasodilator effect. Dobutamine is a synthetic catecholamine. It is a chiral molecule and both (+) and (-) enantiomers are pharmacologically active, but there are important differences in their adrenergic subtype selectivity.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 28 April 2011. After a subsequent national phase, a licence was granted in the UK on 17 May 2011.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Dobutamine 12.5 mg/ml Concentrate for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the active substance(s) (INN)</td>
<td>Dobutamine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Cardiac stimulants excluding cardiac glycosides, adrenergic and dopaminergic agents (C01CA07)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Concentrate for solution for infusion; 12.5 mg/ml</td>
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<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/3913/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria, Belgium, Germany, Estonia, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Portugal and Romania</td>
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<tr>
<td>Marketing Authorisation Number</td>
<td>PL 20568/0037</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Claris Lifesciences UK Limited Golden Gate Lodge Crewe Hall, Weston Road Crewe, Cheshire CW1 6UL</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

Active substance

INN:  Dobutamine hydrochloride
Chemical name:  1,2-Benzenediol, 4-[[3-(4-hydroxyphenyl)-1-methylpropyl] amino] ethyl]-hydrochloride

Structure:

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\text{\begin{center}\includegraphics[width=0.5\textwidth]{structure.png}\end{center}}
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Molecular formula:  C_{18}H_{24}ClNO_{3}
Molecular weight:  337.84
Appearance:  A white or almost crystalline powder, soluble in methanol, sparingly soluble in water and in alcohol.

Dobutamine hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

Confirmation has been provided that the raw materials, intermediates and auxiliary agent used in synthesis of the active substance are not of animal, biological or genetically modified origin.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications and Certificates of Analysis have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning plastic containers and closures for pharmaceutical use, and with legislation relating to primary packaging in contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients sodium metabisulphite (E223), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

Appropriate justification for the inclusion of each excipient has been provided.
All excipients comply with their respective European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the pharmaceutical development programme was to produce a safe, efficacious, product that could be considered a generic medicinal product of the originator product Dobutrex Injection 12.5 mg/ml (Eli Lilly & Company Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to submitting validation data performed on full-scale batches as soon as they are available.

**Control of Finished Product**
The proposed finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is supplied in 20 ml Type I clear glass ampoules in pack sizes of 1 and 5 ampoules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with parenteral products.

**Stability of the product**
Stability studies were performed in accordance with current guidelines, using batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened vials with the storage conditions “Do not store above 25°C.”

After dilution, the following instructions are given concerning shelf-life and storage:
Chemical and physical in-use stability of the diluted product has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, the diluted 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 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

**Bioequivalence**
A bioequivalence study was not necessary to support this application for a parenteral product.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

**MAA form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of dobutamine hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS
No new clinical pharmacology data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for a parenteral product.

Efficacy
No new efficacy data have been submitted with this application and none are required for this type of application.

Safety
No new safety data have been with this application and none are required. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of dobutamine hydrochloride is well-known.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and is in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Dobutamine 12.5 mg/ml Concentrate for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of dobutamine hydrochloride are well-known, no additional data were required.

EFFICACY
No new clinical data were submitted for this application. A bioequivalence study was not necessary to support this application for a parenteral product.

SAFETY
No new safety data were supplied or required for this application. Dobutamine hydrochloride has a well-established safety profile.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with that for the originator product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the originator product, Dobutrex Injection 12.5 mg/ml (Eli Lilly & Company Limited, UK). Extensive clinical experience with dobutamine hydrochloride is considered to have demonstrated its therapeutic value. The benefit/risk ratio is, therefore, considered to be positive.
## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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