Dobutamine®

Dobutamine hydrochloride

Reference labels: Hameln

AfME Markets using same as LPD: Saudi Arabia

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 equivalent to Dobutamine 12.5 mg.

Each vial 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.

Pediatric population

For all pediatric 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 pediatric 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 β-blocking drug. The inotropic effect of dobutamine stems from stimulation of cardiac β_1 receptors and this effect is prevented by β-blocking drugs. However, dobutamine has been shown to counteract the cardiodepressive effects of β-blocking drugs. Conversely, adrenergic blockade may make the β_1 and β_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.

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

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

- reaching the age-predicted maximal heart rate [(220-age in years) x 0.85]

- systolic blood pressure decrease greater than 20 mmHg

- blood pressure increase above 220/120 mmHg

- progressive symptoms (angina pectoris, dyspnoea, dizziness, ataxia)

- progressive arrhythmia (e.g. coupling, ventricular salvos)

- progressive conduction disturbances

- recently developed wall motility disorders in more than 1 wall segment (16-segment model)

- increase of 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.

Pediatric 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 Interaction with other medicinal products and other forms of interaction

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 cycloproprane, 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 $beta_1$ 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 $alpha_1$- and $beta_2$-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 $beta_2$ predominance (see section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Dobutamine did not cause teratogenic effects or affect fertility in trials on rats and rabbits. There have been no studies in humans on use during pregnancy.

Dobutamine should not be used during pregnancy unless the potential benefits to the woman outweigh the potential risks to the fetus.

Use in lactation

There have been no studies in humans on use during lactation. Should it be necessary to administer dobutamine to nursing mothers, breastfeeding should be suspended during the period of exposure.

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

Immune system disorders:

Not Known: Hypersensitivity reactions including rash, fever, eosinophilia and bronchospasm have been reported. Anaphylactic reactions and severe life-threatening asthmatic episodes may be due to 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 ≥ 30 beats/min

Common: Blood pressure increase of ≥ 50 mmHg. Patients suffering from arterial hypertension are more likely to have a higher blood pressure increase.
Blood pressure decrease, ventricular dysrhythmia, dose-dependent ventricular extrasystoles.
Increased ventricular frequency in patients with atrial fibrillation. These patients should be digitalised 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 disorder

Not known: Urinary urgency

Dobutamine stress echocardiography

Cardiac disorders / vascular disorders

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

Common: Supraventricular extrasystoles, ventricular tachycardia

Uncommon: Ventricular fibrillation, myocardial infarction

Very rare: Occurrence of a second degree atrioventricular block, coronary vasospasms.
Hypertensive/hypotensive blood pressure decompensation, occurrence of an intracavitary pressure gradient, palpitations

Not known: Stress cardiomyopathy
Left ventricular outflow tract obstruction
Fatal cardiac rupture

Respiratory system, thoracic and mediastinal disorders

Common: Bronchospasm, shortness of breath

Gastrointestinal disorders

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Exanthema

Very rare: Petechial bleeding

Musculoskeletal and connective tissue disorders

Common: Chest pain

Renal and urinary disorders

Common: Increased urgency at high dosages of infusion

General disorders and administration site conditions

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

Very rare: Cutaneous necrosis

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 marketing authorization 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 according to their local requirements.

To reports any side effect(s):

Saudi Arabia:

The National Pharmacovigilance Centre (NPC):

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext 2317-2356-2340
- SFDA Call Center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

Other GCC States:

 Please contact the relevant competent authority.

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

ATC code C01CA07

Adult population

Dobutamine directly stimulates β-adrenergic receptors and is generally considered a selective β_1-adrenergic agonist, but the mechanisms of action of the drug are complex. It is believed that the β-adrenergic effects result from stimulation of adenyl cyclase activity. In therapeutic doses, dobutamine also has mild β_2 - and α_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 β_1-adrenergic stimulation, experimental evidence suggests that α_1-adrenergic stimulation may also be involved and that the α_1-adrenergic activity results mainly from the (-) -stereoisomer of the drug.

The β_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, 3-0-methydobutamine and by conjugation with glucuronic acid. Conjugates of dobutamine and 3-0-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.

Water for injection.

6.2 Incompatibilities

Dobutamine Hydrochloride Injection when diluted to 250 micrograms/mL and 500 micrograms/mL with 0.9% Sodium Chloride Injection and 5% Glucose Injection, was found to be stable for 24 hours at room temperature and in the presence of fluorescent light.

6.3 Shelf life

24 months

Do not use Dobutamine Hydrochloride after the expiry date which is stated on the Vial label after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Dobutamine Hydrochloride Injection is a sterile solution containing in each 20 mL vial, Dobutamine Hydrochloride 280.2 mg (250 mg Dobutamine equivalent) and Sodium Metabisulfite.

6.6 Special precautions for disposal <and other handling>

Contains no antimicrobial preservative

Following dilution use in one patient on one occasion and discard any residue.

Do not dilute with alkaline solutions

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Hospira Australia Pty Ltd, Australia

MANUFACUTRED BY

Hospira Australia Pty Ltd, Australia

8. MARKETING AUTHORISATION NUMBER(S)

(39-237-98)

9. DATE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

(21-Nov-1998)

10. DATE OF REVISION

August 2018