SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Milrinone 1 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Milrinone is a sterile solution of milrinone lactate equivalent to 1 mg milrinone per ml.

Excipients with known effect: Sodium

This medicinal product contains less than 1 mmol sodium

(23 mg) per dose, i.e. essentially ‘sodium- free’.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion. Clear, colourless to pale yellow liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Milrinone is indicated for the short-term treatment (48 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors).

Children

Milrinone is indicated for the short-term treatment (up to 35 hours) of:

- Severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors),

- Acute heart failure, including low output states following cardiac surgery.

4.2 Posology and method of administration

For intravenous administration only.

For instructions on dilution of the medicinal product before administration, see section 6.6.
Extravenous administration must be avoided. For prevention of local irritation the largest vein should be used. Careful monitoring should be maintained during milrinone therapy including blood pressure, heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function (i.e. serum creatinine). Facilities must be available for immediate treatment of potential adverse cardiac effects (e.g. life-threatening ventricular arrhythmias). The infusion rate should be adjusted according to haemodynamic response.

Length of treatment should be determined on the basis of clinical response. Patients should not be maintained on infusion for more than 48 hours due to a lack of evidence of safety and efficacy in long-term treatment of congestive heart failure (see section 4.4).

Adults:
Milrinone should be given as a loading dose of 50µg/kg administered over a period of 10 minutes usually followed by a continuous infusion at a dosage titrated between 0.375µg/kg/min and 0.75µg/kg/min (standard 0.5 µg/kg/min) according to haemodynamic response and the possible onset of undesirable effects such as hypotension and arrhythmias.
The total dose should not exceed 1.13mg/kg/day total dose.
The following provides a guide to maintenance infusion delivery rate based upon a solution containing milrinone 200µg/ml prepared by adding 400ml diluent per 100ml solution for injection (40ml diluent per 10ml ampoule or respectively 80ml per an ampoule of 20ml).

Maintenance Dose (**microgram** /kg/**min**)	Maintenance Infusion (**microgram** /kg/**hr**)	200µg/ml Delivery Rate (**ml**/kg/**hr**)
0.375	22.5	0.11
0.400	24.0	0.12
0.500	30.0	0.15
0.600	36.0	0.18
0.700	42.0	0.21
0.750	45.0	0.22

Solutions of different concentrations may be used according to patient fluid requirements. The duration of therapy should depend upon the patient's response.

Elderly:
Experience so far suggests that no special dosage recommendations are necessary in patients with normal renal function. Renal clearance may be

reduced in elderly patients, and lower Milrinone doses may be required in such cases.

Renal Impairment:
Dosage adjustment required. Dosage adjustment in patients with renal impairment is based on data obtained from patients with severe renal impairment but without congestive heart failure, who show significant increases to the terminal elimination half-life of milrinone. The loading dose is not affected, but a reduction in the maintenance infusion rate may be necessary depending on the severity (creatinine clearance) of the renal impairment (see table below):

Creatinine Clearance (ml/min/1.73m^2)	Maintenance Dose (**microgram**/kg/min)	200µg/ml Delivery Rate (ml/kg/hr)
5	0.20	0.06
10	0.23	0.07
20	0.28	0.08
30	0.33	0.10
40	0.38	0.11
50	0.43	0.13

Paediatric population:
In published studies selected doses for infants and children were:
- Intravenous loading dose: 50 to 75 µg/kg administered over 30 to 60 minutes.

- Intravenous continuous infusion: To be initiated on the basis of hemodynamic response and the possible onset of undesirable effects between 0.25 to 0.75 µg/kg/min for a period up to 35 hours.

In clinical studies on low cardiac output syndrome in infants and children under 6 years of age after corrective surgery for congenital heart disease 75 µg/kg loading dose over 60 minutes followed by a 0.75 µg/kg/min infusion for 35 hours significantly reduced the risk of development of low cardiac output syndrome.
Results of pharmacokinetic studies (see section 5.2) have to be taken into consideration.

Renal impairment:
Due to lack of data the use of milrinone is not recommended in paediatric population with renal impairment (for further information please see section 4.4).

Patent ductus arteriosus:
If the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.4, 4.8, 5.2, and 5.3).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe hypovolemia.

4.4 Special warnings and precautions for use

Milrinone is not recommended immediately following acute myocardial infarction until safety and efficacy have been established in this situation. The use of positive inotropic agents such as Milrinone in the acute phase of post myocardial infarction may lead to an undesirable increase in myocardial oxygen consumption (MVO_2). Heightened caution is needed in patients in the acute phase of myocardial infarction in spite of milrinone not increasing MVO_2 in patients with chronic heart failure.

Careful monitoring should be maintained during Milrinone therapy including blood pressure, heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function (i.e. serum creatinine). Facilities must be available for immediate treatment of potential adverse cardiac effect (e.g. life-threatening ventricular arrhythmias).

In patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis (KMP), milrinone should not be used in place of surgical relief of the obstruction. As with other drugs with inotropic / vasodilator properties, it may aggravate outflow obstruction in these conditions.

Supraventricular and ventricular arrhythmias have been observed in the high- risk population treated with Milrinone. In some patients an increase in ventricular ectopy including non-sustained ventricular tachycardia has been observed. As the potential for arrhythmia, already prevalent in heart failure, may be increased by many drugs or combination of drugs, patients receiving milrinone should be closely monitored during infusion ***and the infusion should be stopped if arrhythmias develop***.

There is possibility of an increased ventricular response rate in patients with flutter or fibrillation. In these patients, prior digitalisation or treatment with other agents to prolong atrio-ventricular node conduction time should be considered, as Milrinone produces a slight enhancement in A-V node conduction.

Milrinone may induce hypotension as a consequence of its vasodilatory activity, therefore caution should be exercised when Milrinone is administered to patients who are hypotensive prior to treatment. In patients showing excessive decreases in blood pressure after Milrinone administration, the treatment should be discontinued until the hypotensive effect has been resolved and then resumed, if necessary, at a lower rate of infusion.

If prior vigorous diuretic therapy is suspected to have caused significant decreases in cardiac filling pressure, milrinone should be administered with caution while monitoring blood pressure, heart rate, and other clinically relevant symptoms.

Fluid and electrolyte changes, as well as serum creatinine levels should be carefully monitored during treatment. Improvement in cardiac output and consequently, diuresis, may require reduction in the dose of a diuretic agent. Potassium loss due to excessive diuresis may predispose digitalised patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance, of or during, Milrinone use.

Decrease in haemoglobin, including anaemia, often takes place in the setting of cardiac failure. Due to the risk of thrombocytopenia or anaemia, careful monitoring of the corresponding laboratory parameters is required in patients with decreased platelet count or decreased haemoglobin.

There is no experience in controlled trials with infusions of milrinone for periods exceeding 48 hours. Cases of infusion site reaction have been reported with intravenous milrinone therapy (see section 4.8). Consequently, careful monitoring of the infusion site should be maintained so as to avoid possible extravasation.

Paediatric population:

The following should be considered in addition to the warnings and precautions described for adults:

In neonates, following open heart surgery during Milrinone therapy, monitoring should include heart rate and rhythm, systemic arterial blood pressure via umbilical artery catheter or peripheral catheter, central venous pressure, cardiac index, cardiac output, systemic vascular resistance, pulmonary artery pressure, and atrial pressure. Laboratory values that should be followed are platelet count, serum potassium, liver function, and renal function.

Frequency of assessment is determined by baseline values, and it is necessary to evaluate the neonate’s response to changes in therapy.

Literature revealed that in paediatric patients with impaired renal function, there were marked impairment of milrinone clearance and clinically significant side effects, but the specific creatinine clearance at which doses must be adjusted in paediatric patients is still not clear, therefore the use of milrinone is not recommended in this population (see section 4.2).

In paediatric patients milrinone should be initiated only if the patient is hemodynamically stable.

Caution should be exercised in neonates with risk factors of intraventricular haemorrhage (i.e. preterm infant, low birth weight) since milrinone may induce thrombocytopenia. In clinical studies in paediatric patients, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.8).

In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in paediatric population. Therefore, if the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.2, 4.8, 5.2, and 5.3).

Special patient groups:

There are no special recommendations for elderly patients (see section 4.2). No age related effects on the incidence of adverse events have been observed. Controlled pharmacokinetic studies have not shown changes of pharmacokinetic in elderly.

Milrinone should be used with caution in patients with hepatic impairment.

In patients with severe renal impairment dosage adjustment is required (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Incompatibilities: See section 6.2.

Furosemide or bumetanide should not be administered in intravenous lines containing milrinone lactate in order to precede precipitation.

Milrinone should not be diluted in sodium bicarbonate intravenous infusion.

Fluid and electrolyte changes, as well as serum creatinine levels should be carefully monitored during treatment with milrinone. Improvement in cardiac output and consequently, diuresis, may require reduction in the dose of a diuretic agent. Potassium loss due to excessive diuresis may predispose digitalised patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of, or during milrinone use.

Concomitant administration of inotropic agents increases the positive inotropic effects.

4.6 Pregnancy and lactation

Pregnancy:

Although animal studies have not revealed evidence of drug-induced foetal damage or other deleterious effects on reproductive function, the safety of milrinone in human pregnancy has not yet been established. It should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding:

There is insufficient information on the excretion of milrinone in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue Milrinone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy from the woman.

Fertility:

See section 5.3

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Adverse reactions have been ranked under heading of system-organ class and frequency using the following convention: very common (>= 1/10); common (>= 1/100, <1/10); uncommon (>= 1/1,000, <1/100); rare (>= 1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Not known** (cannot be estimated from the available data)
Blood and the lymphatic system disorders:			Thrombocytopenia*			
Immune system disorder:					Anaphylactic shock	
Metabolism and nutrition disorders:			hypokalemia			
Nervous system disorders:		Headaches, usually mild to moderate in severity	Tremor			
Cardiac disorders:		Ventricular ectopic activity Ventricular tachycardia (non sustained or sustained) Supra–ventricular arrhythmias	Ventricular fibrillation Angina pectoris/chest pain		Torsades de pointes	

System Organ Class	**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)
		Hypotension				
Respiratory, thoracic and mediastinal disorders:					Bronchospasm	
Hepato-biliary disorders:			Liver function tests abnormal			
Skin and subcutaneous tissue disorders:					Skin reactions such as rash.	
General disorders and administration site conditions:						Infusion site reaction

**In infants and children, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.4).*

No relationship has been established between the incidence of supraventricular or ventricular arrhythmias, and the plasma level of milrinone. Life threatening arrhythmias are often found to be associated with underlying risk factors such as pre-existing arrhythmias, metabolic anomalies (e.g. hypokalemia), elevated serum digoxin levels or catheter insertion. *Clinical data suggest that milrinone-related arrhythmias are less common in children than in adults.*

Paediatric population:

Nervous system disorders

Not known: intraventricular haemorrhage (see section 4.4)

Congenital, familial, and genetic disorders

Not known: patent ductus arteriosus*** (see section 4.2, 4.4, 5.2, and 5.3)

***The critical consequences of the patent ductus arteriosus are related to a combination of pulmonary overcirculation with consecutive pulmonary oedema and haemorrhage and of reduced organ perfusion with consecutive intraventricular haemorrhage and necrotizing enterocolitis with possible fatal outcome as described in literature.

Long-term safety data for paediatric population are not yet available.

4.9 Overdose

Overdose of intravenous Milrinone may produce hypotension (because of its vasodilatory effect) and cardiac arrhythmia. If this occurs, Milrinone administration should be reduced or temporarily discontinued until the patient's condition stabilises. No specific antidote is known, but general measures for circulatory support should be taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group; CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES; Phosphodiesterase

ATC code C01CE02

Mechanism of action

Milrinone is a positive inotrop and vasodilator with little chronotropic activity. It also improves left ventricular diastolic relaxation.

It differs from digitalis glycosides catecholamines or angiotensin converting enzyme inhibitors in structure and mode of action.

Pharmacodynamic effects

Milrinone is a selective inhibitor of the peak-III- -phosphodiesterase-isoenzym in the cardiac and vascular muscles. It produces slight enhancement of A-V node conduction, but no other significant electro-physiological effects.

Clinical efficacy and safety

In clinical studies milrinone has been shown to produce prompt improvements in the haemodynamic indices of congestive heart failure, including cardiac output, pulmonary capillary wedge pressure and vascular resistance, without clinically significant effect on heart rate or myocardial oxygen consumption.

Haemodynamic improvement during intravenous milrinone therapy is accompanied by clinical symptomatic improvement in congestive cardiac failure, as measured by change in New York Heart Association classification.

Paediatric population:

Literature review identified clinical studies with patients treated for low cardiac output syndrome following cardiac surgery, septic shock or pulmonary hypertension. The usual dosages were a loading dose of 50 to 75 μg/kg administered over 30 to 60 minutes followed by an intravenous continuous infusion of 0.25 to 0.75 μg/kg/min for a period up to 35 hours. In these studies, milrinone demonstrated an increase of cardiac output, a decrease in cardiac filling pressure, ad decrease in systemic and pulmonary vascular resistance, with minimal changes in heart rate and in myocardial oxygen consumption.

Studies of a longer use of milrinone are not sufficient to recommend an administration of milrinone during a period of more than 35 hours.

Some studies explored the paediatric use of milrinone in patients with nonhyperdynamic septic shock (Barton et al., 1996; Lindsay et al., 1998); the effect of milrinone on postbypass pulmonary hypertension after tetralogy of Fallot repair (Chu et al., 2000); the combined effect of nitric oxide and milrinone on pulmonary circulation after Fontan-type procedure (Cai et al., 2008).

The results of these studies were inconclusive. Therefore, the use of milrinone in these indications cannot be recommended.

5.2 Pharmacokinetic properties

In vitro examinations on protein binding showed that 70 - 91% of milrinone is protein-bound in therapeutically relevant plasma concentrations. Six to twelve hours after a consistent conservation infusion of 0.50 microgram/kg/min, the steady state plasma concentrations of milrinone are approximately 200 ng/ml.

After injecting patients with heart insufficiency intravenously with 12.5 microgram/kg to 125 microgram/kg, milrinone had a distribution volume of 0.38 l/kg, a mean terminal elimination half-life of 2.3 hours and a clearance of 0.13 l/kg/h.

After injecting patients with heart insufficiency intravenously with 0.20 microgram/kg to 0.7 microgram/kg, the substance had a distribution volume of approximately 0.45 l/kg, a mean terminal elimination half-life of 2.4 hours and a clearance of 0.14 l/kg/h. These pharmacokinetic parameters were not dose-dependent. In contrast, the area below the plasma concentration time curve was significantly dose-dependent after the injections. It could be shown with the aid of ultracentrifugation that 70% of milrinone are bound to human plasma proteins in plasma concentrations of between 70 and 400 nanogram/ml.

In patients with heart insufficiency, clearance and half-life were prolonged in accordance with their, in contrast to the healthy subjects, impaired renal function. Data of patients with serious renal insufficiency (creatinin clearance = 0 – 30 ml/min) showed that the terminal elimination half-time is prolonged in cases of renal insufficiency.

Metabolism, secretion

Humans largely secrete milrinone in the urine. The most important secretion products in humans are milrinone (83%) and its o-clucuronide metabolite (12%). In healthy subjects, secretion in the urine occurs quickly; approximately 60% of the dose is found within the first two hours of administration, and approximately 90% within the first eight hours. The mean renal clearance of milrinone i.v. is approximately 0.3 l/min; this indicates active secretion.

Paediatric population:

Milrinone is cleared more rapidly in children than in adults, but infants have significantly lower clearance than children, and preterm infants have even lower clearance. As a consequence of this more rapid clearance compared to adults, steady-state plasma concentrations of milrinone were lower in children than in adults. In paediatric population with normal renal function steady-state milrinone plasma concentrations after 6 to 12 hours continuous infusion of 0.5 to 0.75 μg/kg/min were about of 100 to 300 ng/ml.

Following intravenous infusion of 0.5 to 0.75 μg/kg/min to neonates, infants and children after open heart surgery, milrinone has a volume of distribution ranging from 0.35 to 0.9 litres/kg with no significant difference across age groups. Following intravenous infusion of 0.5 μg/kg/min to very preterm infants to prevent systemic outflow after birth, milrinone has a volume of distribution of about 0.5 litres/kg.

Several pharmacokinetic studies showed that, in paediatric population, clearance increases with increasing age. Infants have significantly lower clearance than children (3.4 to 3.8 ml/kg/min versus 5.9 to 6.7 ml/kg/min). In neonates milrinone clearance was about 1.64 ml/kg/min and preterm infants have even lower clearance (0.64 ml/kg/min).

Milrinone has a mean terminal half-life of 2 to 4 hours in infants and children and a mean terminal elimination half-life of 10 hours in preterm infants.

It was concluded that the optimal dose of milrinone in paediatric patients in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared higher than in adults, but that optimal dose in preterms in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared lower than in children.

Patent ductus arteriosus:

Milrinone is cleared by renal excretion and has a volume of distribution that is restricted to extracellular space which suggests that the fluid overload and hemodynamic changes associated with patent ductus arteriosus may have an effect on distribution and excretion of milrinone (see section 4.2, 4.4, 4.8, and 5.3).

5.3 Preclinical safety data

Acute toxicity

After oral administration, the LD_{50} for male mice is 137 mg/kg and for female mice 170 mg/kg, while the LD_{50} for male rats is 91 mg/kg and for female rats 153 mg/kg.

After intravenous administration of milrinone, focal epicardial and endocardial haemorrhages and focal myocardial fibroses (particularly in the papillary muscle and in the endocardial areas) occur in rabbits.

Subacute toxicity

Subacute toxicity was examined in rats and dogs. In dogs, endocardial haemorrhages and myocardial fibroses occurred in all treated groups after cumulative and fractioned administration of milrinone in quantities just above the therapeutic dose.

Subchronic and chronic toxicity

Oral and intravenous application of milrinone to rats, dogs and monkeys lead in therapeutic doses, or in doses just above the therapeutic dose, to myocardial degenerations, fibroses and, particularly in the region of the papillary muscles of the left ventricle, to subendocardial haemorrhages.

Lesions of the coronary vessels, characterised by a periarterial oedema and inflammation, were only observed in dogs.

Carcinogenicity

In long-term trials, no tumour-producing potential was detected in rats and mice. Endocardial haemorrhages and myocardial necroses and fibroses occurred in rats. At the highest dosage, myocardial degenerations and fibroses were detected in mice. In the stomachs of mice, necroses and ulcers were detected.

Mutagenicity

A detailed in vitro and in vivo test on mutagenicity produced negative results.

Fertility/reproductive toxicology

Milrinone, at oral doses of up to 40 times the usual human therapy dose, did not have an effect on the fertility of male and female rats.

Studies of the reproductive toxicology in rats and rabbits did not produce any evidence of a teratogenic action at doses of up to 10 times (oral) and 2.5 times (i.v.) of the usual human therapy dose.

In a study spanning 3 generations (P, F1, F2 generation) of rats treated orally with milrinone, no effect on the development of the animals and their reproductive capacity was detected in the mothers or the descendents, even at the highest dose (40 times the usual human therapy dose).

Embryonic/foetal dose in relation to the mother’s serum concentration:

A diaplacental transmission of milrinone to the foetus is documented in a study of pregnant monkeys which had human therapy doses administered intravenously. The ratio of maternal serum values to foetal serum levels was 4:1.

Juvenile animals:

A preclinical study was performed to clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm foetal rats. Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10, 1 and 0.1mg/kg). The dilating effects of milrinone in the foetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone (10, 1 and 0.1mg/kg) and indomethacin (10 mg/kg) to the mother rat at D21 (near-term) and D19 (preterm). This in vivo study has shown that milrinone induces dose-dependent dilation of the foetal and the postnatal constricted ductus arteriosus.

Dilating effects were more potent with injection immediately after birth than at 1 hour after birth. In addition, study showed that the premature ductus arteriosus is more sensitive to milrinone than the mature ductus arteriosus (see section 4.2, 4.4, 4.8, and 5.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid, glucose anhydrous, water for injection, sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

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

The following active substance(s) or solution for reconstitution/dilution should not be administered simultaneously:

Furosemide or bumetanide should not be administered in intravenous lines containing milrinone lactate since precipitation occurs.

Milrinone must not be diluted in sodium bicarbonate intravenous infusion.

Other drugs should not be mixed with Milrinone until further compatibility data are available.

6.3 Shelf life

3 years when unopened.

The chemical and physical in-use stability has been demonstrated for 72 hours at room temperature (15-25°C) or at refrigerated condition (2-8°C).
From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at (2 °C to 8 °C) unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions (see section 6.3).

Do not freeze.

6.5 Nature and contents of container

Type 1 colourless glass ampoules of 10 ml and 20 ml packed in boxes of 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Infusion solutions diluted as recommended with sodium chloride 4.5 mg/ml (0.45%) sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/ml (5%) should be freshly prepared before use.

For single use only.

The diluted solution should be examined visually for particulate matter and discoloration prior to administration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Stragen UK Limited

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England

8 MARKETING AUTHORISATION NUMBER(S)

PL 21844/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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