Milrinone 1 mg/ml

CONCENTRATE FOR SOLUTION FOR INFUSION

MILRINONE
1mg /ml concentrate for solution for infusion

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

What is in this leaflet

1. WHAT MILRINONE IS AND WHAT IT IS USED FOR

The name of your medicine is Milrinone.
Milrinone contains the active substance called milrinone. This belongs to a group of medicines called phosphodiesterase inhibitors.

It works by making your heart muscle contract more strongly and your blood vessels become wider. This means blood can flow more easily making your heart pump blood more successfully.

Milrinone can be used in adults for:
Short-term treatment of severe congestive heart failure (where the heart cannot pump enough blood to the rest of the body) when other medicines have not worked.

Milrinone can be used in children for short term treatment (up to 35 hours) of:
- Severe congestive heart failure (where the heart cannot pump enough blood to the rest of the body) when other medicines have not worked
- Acute heart failure after a heart operation i.e. when your heart is having difficulty pumping blood around your body.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN MILRINONE

Do not use Milrinone:
- if you are allergic to milrinone or any of the other ingredients of this medicine (listed in section 6)
- if you suffer from low blood volume

Warnings and precautions
Talk to your doctor or nurse before you are given Milrinone:
- if you have an acute heart infarct
- if you have uneven or uncontrolled fast heartbeats. You may also be experiencing pounding in your chest, light-headedness, fainting and shortness in breath
- if you have low blood pressure which may make you feel dizzy, light-headed or faint
- if you have previously taken water tablets (diuretics) which caused you to have heart problems
- if you have low levels of potassium in your blood. Your doctor may do blood tests to check this
- if you have an abnormal drop in the number of blood cells involved in forming blood clots (thrombocytopenia) and/or a reduced haemoglobin concentration
- if you have kidney problems
- if you have liver problems

Children:
The following should be considered in addition to warnings and precautions described for adults:
Before giving Milrinone infusion, your doctor will check a lot of parameters such as heart rhythm and blood pressure. He/she will order blood tests as well.
The infusion will not start if your child's heart rhythm and blood pressure is not stable.

Please tell your doctor if:
- your child has kidney problems
- your child is a preterm infant or has a low birth weight
- your child has a certain heart problem named Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed.

In these cases, your doctor will decide if your child will be treated with Milrinone.

Other medicines and Milrinone
Tell your doctor or nurse if you are taking or have recently taken any other medicines.
This is because milrinone can affect the way some other medicines work. Also some medicines can affect the way milrinone works.

In particular, tell your doctor or nurse if you are taking:
- Digoxin (used for heart problems)
- Other heart medication that affects the contractions of the heart muscle (inotropic agents).
- Water tablets (diuretics)
- Medicines used to treat high blood pressure or angina (chest pain) such as amlodipine, nifedipine or felodipine.

Milrinone with food and drink
Not known.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
In general you will be given Milrinone while you are hospitalised as careful clinical monitoring of the therapy is recommended. Thus the effect on the ability to drive and to use machines is not known.

3. HOW MILRINONE IS GIVEN

Milrinone will always be given by your doctor or nurse. This is because it needs to be given as an infusion. It is administered into a vein. Your doctor will decide on the correct dose, based on the nature of your symptoms. Milrinone is intended for use in hospitals only.
Tests:
During injection, your doctor or nurse will use an electrocardiogram (ECG) to check how well your heart works. They will also carry out blood tests and check your blood pressure and pulse rate.

How this medicine will be given to you
- This medicine is usually given in a "drip" after being diluted using either a sugar or a salt solution
- If you feel the effect of your medicine is too weak or to strong, tell your doctor or nurse.

The recommended dose is
Adults
- Your doctor will decide how much medicine you should have based on your body weight

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THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

Milrinone 1mg /ml concentrate for solution for infusion
Please see SmPC for complete information

Preperation and other Handling
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.
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 stored at (2 °C to 8 °C) unless dilution has taken place in controlled and validated aseptic conditions. Any unused product or waste material should be disposed of in accordance with local requirements.

Safety Information:
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. creatinine).

Incompatibilities:
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.

Administration:
For intravenous administration only. 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.

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).

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- If you have problems with your kidneys, you might be given a lower dose Milrinone infusions are given over a maximum of 48 hours.

Use in children
- Your doctor should give your child a first dose ranging between 50 and 75 micrograms for every kilogram of his weight, over a period of 30 to 60 minutes.
- This is then followed by a dose ranging from 0.25 to 0.75 micrograms for every kilogram of his/her weight per minute according to your child's response to the treatment and occurrence of side effects. Milrinone can be given for up to 35 hours. During infusion, your child will be closely monitored: your doctor will check a lot of parameters such as heart rhythm and blood pressure and blood will be taken to evaluate the response to therapy and occurrence of side effects.

If you are given more Milrinone than you should
Always ask if you are not sure why you are getting a dose of medicine. The following effects may happen if you had too much Milrinone: feeling dizzy, light-headedness and fainting (due to low blood pressure) and an uneven heartbeat.

If you forget to use Milrinone
If you think you have missed a dose, tell your doctor or nurse.
If you have further questions on the use of this medicine, ask your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

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

Stop having Milrinone and tell your doctor straight away if:
You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. The chances of this happening are very rare.

Tell your doctor or nurse straight away if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- Uneven, increased or fast heartbeats. You may also experience pounding in your chest, feellight-headedness, faint or short of breath
- Headaches: Mild to moderate in most cases
- Low blood pressure: Signs of this include feeling dizzy, light-headedness or fainting. If you also notice signs like a fast or uneven heartbeat or chest pain this could be a more serious side effect (see above)

Uncommon (may affect up to 1 in 100 people)
- Ventricular fibrillation – a serious heart rhythm problem. Signs of this include very fast, uneven or forceful heartbeat (palpitations), dizziness and loss of consciousness. You may also feel sick; have cold sweat, shortness in breath and chest pain
- Thrombocytopenia – a blood problem (lack of blood platelets). Signs of this are that you may bruise more easily than usual
- Chest pain
- Hypokalemia, where your blood's potassium level is low. Signs of this are tiredness,confusion, muscle weakness and muscle cramps
- Muscle contractions (tremor)
- A blood test may show changes in the way your liver is working

Very Rare (may affect up to 1 in 10,000 people)
- Torsades de Points - a serious heart rhythm problem. Signs of this include very fast, uneven or forceful heartbeats (palpitations), dizziness and loss of consciousness. You may also feel sick, have cold sweats, shortness of breath, unusual pale complexion and chest pain
- Difficulties breathing, wheezing or tightness in the chest
- Skin reactions

Not known (frequency cannot be estimated from the available data)
- Reduction of red blood count and/or haemoglobin concentration
- Irritation at the infusion side.

Additional side effects in children
In addition to side effects observed in adults, the following were reported in children:
Frequency not known:
- bleeding into the fluid-filled areas (ventricles) surrounded by the brain (intraventricular haemorrhage)
- a heart problem known as Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed. This can cause excess fluid in the lungs, bleedings, destruction of the bowel or part of the bowel and possibly be fatal. Moreover, compared to adults, decrease in the number of platelets in the blood seems to occur more often in children and the risk of this side effect is increased with the duration of the Milrinone infusion. Heart rhythm troubles seem to occur less often in children than in adults.

Reporting of side effects
If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard
By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE MILRINONE

This medicine will be kept by your doctor or nurse in a safe place out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the ampoule and the carton after EXP. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Do not freeze.
For single use only.
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).
Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Milrinone contains
- Milrinone is a sterile solution of milrinone lactate equivalent to 1mg milrinone per ml.
- The other ingredients are lactic acid, glucose anhydrous, water for injection and sodium hydroxide (for pH adjustment).

What Milrinone looks like and contents of the pack
Milrinone is a clear, colourless to pale yellow liquid.
Milrinone is available as 10 ml and 20 ml glass ampoules in boxes of 10.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
STRAGEN UK Limited - Castle Court, 41 London Road, Reigate, Surrey RH2 9RJ, England
Tel.: +44 (0) 870 351 8744, Fax.: +44 (0) 870 351 8745
E-mail: info@stragenuk.com
Manufacturer:
CENEXI - 52, rue Marcel et Jacques Gaucher, 94120 Fontenay-Sous-Bois France

This medicinal product is authorised in the Member States of the EEA under the following names:

Germany	Milrinon Stragen, 1mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Milrinone Stragen
Netherlands	Milrinon Stragen
United Kingdom	Milrinone

This leaflet was last revised in 27.02.2014

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

Children:
In published studies selected doses for infants and children were:
- Intravenous loading dose: 50 to 75µg/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 0.75µg/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 75µg/kg loading dose over 60 minutes followed by a 0.75µg/kg/min infusion for 35 hours significantly reduced the risk of development of low cardiac output syndrome.
Results of pharmacokinetic studies 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.

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.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients
- Severe hypovolemia

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.