PACKAGE LEAFLET: INFORMATION FOR THE USER

Milrinone 1 mg/ml Solution for Injection/Infusion

milrinone

Read all of this leaflet carefully before you start taking 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, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. 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 1 mg/ml Solution for Injection/Infusion (referred to as Milrinone throughout this leaflet). It contains a medicine 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
- Treatment after a heart operation for when your heart is having difficulty pumping blood around your body

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
- short term treatment (up to 35 hours) of 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

You should not be given Milrinone if:
- you are allergic (hypersensitive) to milrinone or any of the other ingredients of this medicine (listed in Section 6). Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- you have lost body fluids and are severely dehydrated.

Do not have this medicine if any of the above apply to you. If you are not sure, talk to your doctor, nurse or pharmacist before having Milrinone.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before you are given milrinone if you:
- are having or have just had a heart attack
- have severe heart valve problems such as narrowing, thickening or blockage of your heart valves
- have uneven or uncontrolled fast heartbeats. You may also be experiencing pounding in your chest, light-headedness, fainting and shortness in breath
- have low blood pressure which may make you feel dizzy, light-headed or faint
- have previously taken water tablets (diuretics) which caused you to have heart problems
- have low levels of potassium in your blood. Your doctor may do blood tests to check this
- have kidney problems

If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before having Milrinone.

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

Children and adolescents
Before giving Milrinone, 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
- is a preterm infant or has a low birth weight
- has a certain heart problem named Patent Ductus Arteriosus: a connection between two 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
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal 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, nurse or pharmacist if you are taking:
- digoxin (used for heart problems)
- water tablets (diuretics)
- medicines used to treat high blood pressure or angina (chest pain) such as amlodipine, nifedipine or felodipine.

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

Milrinone contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. HOW YOU WILL BE GIVEN MILRINONE

Milrinone will always be given by your doctor or nurse. This is because it needs to be given as an injection. It is administered into a vein.

Having this medicine
- This medicine is usually given in a 'drip' after being diluted using either 0.45% sodium chloride infusion, 0.9% sodium chloride infusion or 5% glucose infusion
- If you feel the effect of your medicine is too weak or too strong, tell your doctor or nurse

How much will be given to you
- Your doctor will decide how much medicine you should have based on your body weight
- If you have problems with your kidneys, you may be given a lower dose

Adults and the elderly
- Your doctor should give you a first dose of 50 micrograms for every kilogram of your weight over a period of 10 minutes
- This is then followed by a smaller dose between 0.375 and 0.75 micrograms for every kilogram of body weight per minute, as needed
- The medicine is usually given for 2 to 3 days, but it may be given for up to 5 days
- If you are having this medicine after a heart operation, it will usually only be given for up to 12 hours

Use in children and adolescents
- 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 receive more Milrinone than you should
It is unlikely that your doctor or nurse will give you too much of this medicine. Your doctor and nurse will check your progress and the medicine that you are given. Always ask if you are not sure why you are getting a dose of medicine. The following effects may happen if you have too much Milrinone: feeling dizzy, light-headedness and fainting (due to low blood pressure) and an uneven heartbeat.

If you miss a dose of Milrinone
Your doctor or nurse will have instructions on when to give you this medicine. It is unlikely that you will not be given the medicine as it has been prescribed. However, if you do think you have missed a dose, tell your doctor or nurse.

If you stop having Milrinone
Keep having Milrinone until your doctor tells you to stop. Do not stop having Milrinone just because you feel better. If you stop, your illness may get worse.

Tests
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.

If you have any 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, fainting or losing consciousness. The chances of this happening are very rare

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

Common (affects less than 1 in 10 people)
- Uneven, increased or fast heartbeats. You may also experience pounding in your chest, feel light-headed, faint or short of breath

Uncommon (affects less than 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 sweats, shortness of breath and chest pain
- Thrombocytopenia – a blood problem. Signs of this are that you may bruise more easily than usual
- Chest pain

Very rare (affects less than 1 in 10,000 people)
- Torsades de Pointes – 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 sweats, shortness of breath, unusual pale complexion and chest pain
- Difficulty breathing, wheezing or tightness in the chest

Tell a doctor or nurse as soon as possible if you notice any of the following side effects:
Common (affects less than 1 in 10 people)
- Low blood pressure. Signs of this include feeling dizzy, lightheaded 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)
- Headache

Uncommon (affects less than 1 in 100 people)
- Feeling shaky
- Low levels of potassium in your blood. Signs of this are tiredness, confusion, muscle weakness and muscle cramps. This may be due to low levels of potassium in your body.

Tell a doctor or nurse if any of the following side effects gets serious or lasts longer than a few days

Very Rare (affects less than 1 in 10,000 people)
- Skin rashes including at the site of the injection

Uncommon (affects less than 1 in 100 people)
- A blood test may show changes in the way the liver is working

Talk to your doctor, nurse or pharmacist if any of the side effects gets serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

In addition to side effects observed in adults, the following were reported in children and adolescents:

Additional side effects in children and adolescents

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 two 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
- Changes in the way the kidneys are working if you already have low blood pressure.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting systems listed below:

Ireland:
HPRA Pharmacovigilance, Website: www.hpra.ie.
Malta:
ADR reporting, Website: www.medicinesauthority.gov.mt/adrportal.

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE MILRINONE

- Keep this medicine out of the sight and reach of children
- This medicine is for single use; any unused contents should be discarded
- This medicine should not be used after the expiry date which is stated on the carton and ampoule label after 'EXP'. The expiry date refers to the last day of that month
- Store below 25°C. Do not freeze.
- After dilution: Diluted solutions of Milrinone have been shown to be chemically and physically stable when stored for 48 hours at 5°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
- Do not throw away any medicines via wastewater or household waste. 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
The active substance is: milrinone. Each ml of solution contains 1 mg milrinone. Each 10 ml ampoule contains 10 mg milrinone.
The other ingredients are: (S)-lactic acid, anhydrous glucose, water for injections and the pH adjusters sodium hydroxide and lactic acid (see end of section 2).

What Milrinone looks like and contents of the pack
Milrinone is a clear, colourless to pale yellow, sterile solution, practically free from particles. It is supplied in 10 ml clear, neutral glass (Type I, PhEur) ampoules. It is available in packs of ten ampoules.

Marketing Authorisation Holder in Ireland and Malta
Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co. Tipperary, Ireland.

Manufacturer
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, United Kingdom.

Other sources of information

To listen to or request a copy of this leaflet in Braille, large print or audio please call +44 1978 661261. Please be ready to give the following information:

Product name	**Reference number**
Milrinone 1 mg/ml Solution for Injection/Infusion	PA 0281/244/001 MA 143/04201

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

United Kingdom, Ireland and Malta: Milrinone 1 mg/ml Solution for Injection/Infusion

This leaflet was last revised in 04/2022

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Milrinone 1 mg/ml Solution for Injection/Infusion
Please refer to the Summary of Product Characteristics (SmPC) for further details on this product.

Qualitative and Quantitative Composition
Each ml of solution contains 1 mg milrinone. Each 10 ml ampoule contains 10 mg milrinone.

Pharmaceutical Form
Solution for injection/infusion.

Clear, colourless to pale yellow solution, practically free from particles.

The pH of the solution is 3.2 - 4.0 and the osmolality is 261 – 319 mOsm/Kg.

Therapeutic Indications
Milrinone Injection is indicated for the short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy, and for the treatment of patients with acute heart failure, including low output states following cardiac surgery.

In paediatric population 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), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.

Posology and method of administration
For intravenous administration.

Adults: Milrinone Injection should be given as a loading dose of 50 µg/kg administered over a period of 10 minutes usually followed by a continuous infusion at a dosage titrated between 0.375 µg/kg/min and 0.75 µg/kg/min according to haemodynamic and clinical response, but should not exceed 1.13 mg/kg/day total dose. For instructions on dilution of the product before administration and a guide to maintenance infusion delivery rates, see the information under “Special precautions for disposal and other handling”.

Solutions of different concentrations may be used according to patient fluid requirements. The duration of therapy should depend upon the patient's response. In congestive cardiac failure, patients have been maintained on the infusion for up to 5 days, although the usual period is 48 to 72 hours. In acute states following cardiac surgery, it is unlikely that treatment need be maintained for more than 12 hours.

Renal Impairment: Dosage adjustment required. Data obtained from patients with severe renal impairment but without heart failure have demonstrated that the presence of renal impairment significantly increases the terminal elimination half-life of milrinone. For patients with clinical evidence of renal impairment, the loading dose is not affected, but the infusion rate should be adjusted according to haemodynamic response. Recommended maintenance infusion rates are provided under “Special precautions for disposal and other handling”.

Elderly: Experience so far suggests that no special dosage recommendations are necessary.

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 of the SmPC) 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 of the SmPC).

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 sections 4.4, 4.8, 5.2, and 5.3 of the SmPC).

Pharmaceutical Particulars

List of excipients

(S)-Lactic Acid
Anhydrous Glucose
Water for Injections
Sodium Hydroxide (for pH adjustment)
Lactic Acid (for pH adjustment)

Incompatibilities

Furosemide or bumetanide should not be administered in intravenous lines containing Milrinone Injection since precipitation occurs on admixture. Sodium Bicarbonate Intravenous infusion should not be used for dilution.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life
3 years for the unopened product

After dilution
Chemical and physical in-use stability has been demonstrated for 48 hours at 5°C when diluted with 0.45% sodium chloride infusion, 0.9% sodium chloride infusion or 5% glucose infusion.

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 dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store below 25°C. Do not freeze.

For storage conditions of the medical product after dilution, please refer to the information above, under "Shelf life".

Nature and contents of container

Milrinone 1 mg/ml Solution for Injection/Infusion is presented in 10 ml clear, neutral glass (PhEur, Type I) ampoules. The ampoules are packed in a PVC tray and cardboard box in packs of 10.

Special precautions for disposal and other handling

Instructions for dilution:

Infusion solutions should be freshly prepared before use. Parenteral drug products should be examined visually and should not be used if particulate matter or discolouration are present.

The following diluents may be used to prepare solutions for infusion:

0.45% sodium chloride infusion
0.9% sodium chloride infusion
5% glucose infusion

A solution containing 200 µg/ml milrinone should be prepared by taking the contents of a 10 ml ampoule and adding 40 ml of one of the above diluents (400 ml diluent per 100 ml Milrinone Injection).

For single use. Discard any unused solution.

Delivery rates:

Adults:
The following provides a guide to maintenance infusion delivery rate based upon a solution containing milrinone 200 µg/ml, prepared as described above.

Milrinone Injection Dose (µg /kg/min)	**Infusion Delivery Rate (ml/kg/hr)**
0.375	0.11
0.400	0.12
0.500	0.15
0.600	0.18
0.700	0.21

Renal impairment:
The following maintenance infusion rates are recommended using the infusion solution described above.

Creatinine Clearance (ml/min/1.73m^2)	**Milrinone Injection Dose (µg/kg/min)**	**Maintenance Infusion 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

The infusion rate should be adjusted according to haemodynamic response. See the information under "Posology and method of administration."

Marketing Authorisation Holder in Ireland and Malta

Pinewood Laboratories Ltd.,
Ballymacarbry,
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Co. Tipperary,
Ireland.

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