

## **DATA SHEET**

### **1 PRIMACOR 1 MG/ML SOLUTION FOR INJECTION**

PRIMACOR 1 mg/mL solution for injection

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each single-dose ampoule contains 1 mg/mL milrinone (as lactate)

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Solution for injection

Clear, colourless to pale yellow solution.

The pH is between 3.2 and 4.0.

### **4 CLINICAL PARTICULARS**

#### **4.1 THERAPEUTIC INDICATIONS**

PRIMACOR is indicated for the short term intravenous therapy of severe congestive heart failure. The majority of experience with intravenous PRIMACOR has been in patients receiving digoxin and diuretics.

PRIMACOR is also indicated for low output states following cardiac surgery, including weaning from cardio-pulmonary bypass pump.

#### **4.2 DOSE AND METHOD OF ADMINISTRATION**

PRIMACOR should be administered with a loading dose followed by a continuous infusion (maintenance dose) according to the following guidelines:

### Loading dose

50 mcg/kg administered slowly over 10 minutes

### Maintenance dose

Table 1

	INFUSION RATE	TOTAL DAILY DOSE (24 HOURS)
MINIMUM	0.375 mcg/kg/min	0.60 mg/kg
STANDARD	0.50 mcg/kg/min	0.77 mg/kg
MAXIMUM	0.75 mcg/kg/min	1.13 mg/kg

Note: Administer as a continuous intravenous infusion.

The infusion rate should be adjusted according to haemodynamic and clinical response. Patients should be closely monitored. Most patients show an improvement in haemodynamic status as evidenced by increases in cardiac output and reductions in pulmonary capillary wedge pressure.

Note: See "Dosage Adjustment in Renally Impaired Patients".

Dosage may be titrated to the maximum haemodynamic effect and should not exceed 1.13 mg/kg/day. Duration of therapy should depend upon patient responsiveness.

Intravenous infusions of PRIMACOR should be administered as described in Table 2.

Table 2 - PRIMACOR - Rates of Infusion for concentrations of 100 mcg/mL, 150 mcg/mL and 200 mcg/mL. Infusion Delivery Rate

PRIMACOR (mcg/kg/min)	100 mcg/mL (mL/kg/hr)	150 mcg/mL (mL/kg/hr)	200 mcg/mL (mL/kg/hr)
0.375	0.22	0.15	0.11
0.400	0.24	0.16	0.12
0.500	0.30	0.20	0.15
0.600	0.36	0.24	0.18
0.700	0.42	0.28	0.21
0.750	0.45	0.30	0.22

In order to calculate flow rate (mL/hr) multiply infusion delivery rate by patient weight (in kg).

These ampoules require preparation of dilutions prior to administration to patients intravenously.

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

### **Dosage Adjustment in Renally Impaired Patients**

Data obtained from patients with severe renal impairment (creatinine clearance = 0 to 30 mL/min) but without congestive heart failure have demonstrated that the presence of renal impairment significantly increases the terminal elimination half-life of milrinone. Reductions in the starting infusion rate may be necessary in patients with renal impairment. For patients with clinical evidence of renal impairment, the recommended infusion rate can be obtained from Table 3:

**Table 3**

<b>CREATININE CLEARANCE (mL/min/1.73m<sup>2</sup>)</b>	<b>INFUSION RATE (mcg/kg/min)</b>
5	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

### **4.3 CONTRAINDICATIONS**

PRIMACOR should not be used in patients with severe obstructive aortic or pulmonary valvular disease, or hypertrophic subaortic stenosis. PRIMACOR should not be used in lieu of surgical relief of the obstruction. Like other inotropic agents, PRIMACOR may aggravate outflow tract obstruction in these conditions.

Hypersensitivity to milrinone, other bipyridines or any other ingredient in the formulation listed in section 6.1.

### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

#### **Warnings**

Myocardial ischaemia or infarction may occur in patients following cardiac surgery. Should these events occur, care should be taken with the use of PRIMACOR as information on the safety of PRIMACOR under these circumstances is limited.

### ***Use in Acute Myocardial Infarction***

Use of inotropic agents such as milrinone during the acute phases of a myocardial infarction may lead to an undesirable increase in myocardial oxygen consumption (MVO<sub>2</sub>). Milrinone has not increased MVO<sub>2</sub> in patients with chronic heart failure, however, until further clinical experience with this class of drugs is gained, PRIMACOR is not recommended during the acute phase of post myocardial infarction.

### **Precautions**

Supraventricular and ventricular arrhythmias have been observed in the high-risk population treated. In some patients, PRIMACOR has been shown to increase ventricular ectopy, including non-sustained ventricular tachycardia. The potential for arrhythmia, present in congestive heart failure itself, may be increased by many drugs or combinations of drugs. Patients receiving PRIMACOR should be closely monitored (including heart rate, clinical state, electro-cardiogram, fluid balance, electrolytes and renal function) during infusion.

PRIMACOR produces a slight shortening in A-V node conduction time, indicating a potential for an increased ventricular response rate in patients with atrial flutter/fibrillation which is not being controlled with digitalis therapy. In these patients, prior digitalisation or treatment with other agents to prolong A-V node conduction time should be considered.

PRIMACOR may induce hypotension as a consequence of its vasodilatory action. Caution should therefore be exercised in patients with hypotension prior to treatment or in those showing excessive decreases in blood pressure during therapy with milrinone lactate. In such cases, the infusion should be stopped until the hypotensive effect has been resolved, then resumed at a lower rate if resumption is considered necessary.

If prior vigorous diuretic therapy is suspected to have caused significant decreases in cardiac filling pressure, PRIMACOR should be cautiously administered with monitoring of blood pressure, heart rate, and clinical symptomatology.

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.

Fluid and electrolyte changes, as well as serum creatinine levels and renal function should be carefully monitored during PRIMACOR therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalised patients to arrhythmias. Therefore, hypokalaemia should be corrected by potassium supplementation in advance of or during PRIMACOR use.

### ***Use in Elderly Patients***

There are no special dosage recommendations for the elderly patient.

Ninety percent of all patients administered PRIMACOR in clinical studies were within the age range of 45-70 years, with a mean age of 61 years. Patients in all age groups demonstrated clinically and statistically significant responses. No age-related effects on the incidence of adverse reactions have been observed.

Controlled pharmacokinetic studies have not disclosed any age-related effects on the distribution and elimination of PRIMACOR.

### ***Use in Renal Impairment***

In patients with severe renal impairment the dose should be adjusted (see section 4.2).

### ***Paediatric population***

Safety and effectiveness in children have not been established.

## **4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

No untoward clinical manifestations have been observed in patients in whom PRIMACOR was used concurrently with the following drugs: digitalis glycosides, lignocaine, quinidine, hydralazine, prazosin, isosorbide dinitrate, glyceryl trinitrate, chlorthalidone, frusemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, diazepam, insulin, and potassium supplements.

See section 6.2 for incompatibility information.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Pregnancy**

Category B3

Oral administration of PRIMACOR to pregnant rats and rabbits during organogenesis produced no evidence of teratogenicity at dose levels up to 40 mg/kg/day and 12 mg/kg/day respectively. PRIMACOR did not appear to be teratogenic when administered intravenously to pregnant rats at doses up to 3 mg/kg/day or pregnant rabbits at doses up to 12 mg/kg/day, although an increased resorption rate was apparent at dose levels above 3 mg/kg/day (intravenous) in the latter species. There are no adequate and well-controlled studies in pregnant women. PRIMACOR should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### **Breast-feeding**

Caution should be exercised when PRIMACOR is administered to nursing women since it is not known whether it is excreted in human milk.

## **Fertility**

In reproductive performance studies in rats, PRIMACOR had no effect on male or female fertility at oral doses up to 32 mg/kg/day.

## **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

## **4.8 UNDESIRABLE EFFECTS**

### **Cardiovascular Effects**

Ventricular arrhythmias were reported in 12.1% of patients receiving PRIMACOR: Ventricular ectopic activity, 8.5%; non-sustained ventricular tachycardia, 2.8%; sustained ventricular tachycardia 1% and ventricular fibrillation, 0.2%. Holter recordings have demonstrated in some patients that injection of PRIMACOR increases ventricular ectopy, including nonsustained ventricular tachycardia. Life-threatening arrhythmias are infrequent and when present have been associated with certain underlying factors such as pre-existing arrhythmias, metabolic abnormalities (eg. hypokalaemia), abnormal digoxin levels and catheter insertion.

Very rarely (< 0.01%) cases of torsades de pointes have been reported.

Supraventricular arrhythmias were reported in 3.8% of the patients receiving PRIMACOR. The incidence of both supraventricular and ventricular arrhythmias has not been related to the dose or plasma level of milrinone. There is no evidence for a patient subset which is at higher risk for ventricular arrhythmias.

Other cardiovascular adverse reactions include hypotension 2.9% and angina/chest pain 1.2%.

### **CNS Effects**

Headaches, mostly mild to moderate in severity, have been reported in 2.9% of patients receiving PRIMACOR.

### **Skin**

Dermatological reactions such as rashes have been observed in < 0.01% of patients. Cases of infusion site reaction have been reported.

### **Liver**

Abnormal liver function tests have been observed in < 1% of patients.

## **Congenital, Familial, and Genetic Disorders**

Patent ductus arteriosus has been reported.

## **Renal and Urinary Disorders**

Renal failure, secondary to a concomitant hypotension, has been reported.

## **Other Effects**

Other adverse reactions reported, all with an incidence of less than 1% but not definitely related to the administration of PRIMACOR include hypokalaemia, tremor, and thrombocytopenia. Very rarely (< 0.01%) bronchospasm and anaphylactic shock have occurred.

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## **4.9 OVERDOSE**

Doses of PRIMACOR may induce hypotension because of its vasodilator effect. If this occurs, administration of PRIMACOR 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.

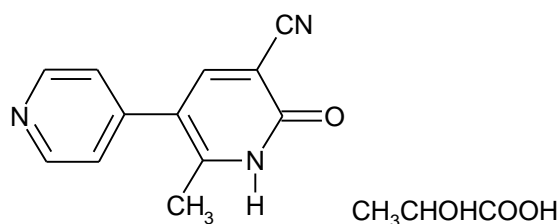
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# **5 PHARMACOLOGICAL PROPERTIES**

## **5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Cardiac therapy, Phosphodiesterase inhibitor. ATC code: CO1CE02

PRIMACOR, brand of milrinone lactate, is a member of a new class of bipyridine inotropic/vasodilator agents with phosphodiesterase activity, distinct from digitalis glycosides or catecholamines. PRIMACOR (milrinone lactate) is designated chemically as 1,6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile lactate and has the following structure.



Milrinone is an off-white to tan crystalline compound with a molecular weight of 211.2 and an empirical formula of C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O. It is stable and colourless to pale yellow in solution. PRIMACOR is available as sterile aqueous solutions of the lactate salt of milrinone for injection or infusion intravenously.

### Mechanism of action

PRIMACOR is a positive inotrope and vasodilator, with little chronotropic activity, different in structure and mode of action from either the digitalis glycosides or catecholamines.

PRIMACOR, at relevant inotropic and vasorelaxant concentrations, is a selective inhibitor of peak III cAMP phosphodiesterase isozyme in cardiac and vascular muscle. This inhibitory action is consistent with cAMP mediated increases in intracellular ionised calcium and contractile force in cardiac muscle, as well as with cAMP dependent contractile protein phosphorylation and relaxation in vascular muscle. Additional experimental evidence also indicates that PRIMACOR is not a β-adrenergic agonist, and unlike digitalis glycosides, it does not inhibit Na<sup>+</sup>/K<sup>+</sup> ATPase activity.

Clinical studies in patients with congestive heart failure have shown that PRIMACOR produces dose-related and plasma level-related increases in the maximum rate of increase of left ventricular pressure (dP/dt max). Studies in normal subjects have shown that PRIMACOR produces increases in the slope of the left ventricular pressure-dimension relationship, indicating a direct inotropic effect of the drug.

PRIMACOR also produces dose-related and plasma concentration-related increases in forearm blood flow in patients with congestive heart failure, indicating a direct arterial vasodilator activity of the drug.

Both the inotropic and vasodilatory effects have been observed over the therapeutic range of plasma milrinone concentrations of 100 ng/mL to 300 ng/mL.

In addition to increasing myocardial contractility, PRIMACOR improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation.

### Pharmacodynamic effects

In patients with depressed myocardial function, PRIMACOR produces a prompt increase in cardiac output and decreases in pulmonary capillary wedge pressure and vascular resistance, without a significant increase in heart rate or myocardial oxygen consumption.



These haemodynamic improvements are both dose and plasma milrinone concentration related. Haemodynamic improvement during intravenous therapy with PRIMACOR was accompanied by clinical symptomatic improvement, as measured by changes in New York Heart Association classification. The great majority of patients experience improvements in haemodynamic function within 5 to 15 minutes of the initiation of therapy.

In studies in congestive heart failure patients, PRIMACOR when administered as a loading injection followed by a maintenance infusion produced significant mean initial increases in cardiac index as presented in Table 4:

**Table 4**

<b>Cardiac Index</b>	<b>Loading Injection (mcg/kg)</b>	<b>Maintenance Infusion (mcg/kg/min)</b>
25	37.5	0.375
38	50	0.500
42	75	0.750

Over the same range of loading injections and maintenance infusions, pulmonary capillary wedge pressure significantly decreased by 20%, 23% and 36%, respectively, while systemic vascular resistance significantly decreased by 17%, 21% and 37%. The heart rate was generally unchanged (increases of 2%, 3% and 10%, respectively). Mean arterial pressure fell by up to 5%, at the two lower dose regimens, but by 17% at the highest dose. Patients evaluated for 48 hours maintained improvements in haemodynamic function, with no evidence of diminished response (tachyphylaxis). A smaller number of patients have received infusions of PRIMACOR for periods up to 72 hours without evidence of tachyphylaxis.

PRIMACOR has a favourable inotropic effect in fully digitalised patients without causing signs of glycoside toxicity. Theoretically, in cases of atrial flutter/fibrillation, it is possible that PRIMACOR may increase ventricular response rate because of its slight enhancement of AV node conduction. In these cases, digitalis should be considered prior to the institution of therapy of PRIMACOR.

Improvement in left ventricular function and relief of congestive heart failure symptoms in patients with ischaemic heart disease have been observed. The improvement has occurred without inducing symptoms or ECG signs in myocardial ischaemia.

The steady-state milrinone plasma levels after approximately 6-12 hours of unchanging maintenance infusion of 0.50 mcg/kg/min are approximately 200 ng/mL. Near maximal favourable effects of PRIMACOR on cardiac output and pulmonary capillary wedge pressure are seen at plasma milrinone concentrations in the 150 ng/mL to 250 ng/mL range.

### **Clinical efficacy and safety**

In a double-blind, placebo controlled study in patients being weaned off cardiopulmonary bypass, 100% of patients taking PRIMACOR were successfully weaned off bypass compared to 33% of

the placebo arm patients. All patients who initially failed blinded placebo treatment were successfully weaned from cardiopulmonary bypass support following administration with open-label PRIMACOR.

In acute states following cardiac surgery, it is unlikely that treatment need be maintained for more than 12 hours.

## **5.2 PHARMACOKINETIC PROPERTIES**

### **Distribution**

Following intravenous loading, injections of 12.5 to 125.0 mcg/kg to congestive heart failure patients, PRIMACOR has a volume of distribution of 0.38 litres/kg, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 litres/kg/hr. Following intravenous infusions of 0.20 to 0.70 mcg/kg/min to congestive heart failure patients, PRIMACOR has a volume of distribution of about 0.45 litres/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14 litres/kg/hr. These pharmacokinetic parameters were not dose-dependent, and the area under the plasma concentration versus time curve following loading injections was significantly dose-dependent.

PRIMACOR has been shown (by equilibrium dialysis) to be approximately 70% bound to human plasma protein.

### **Biotransformation**

The primary route of excretion of PRIMACOR in man is via the urine, with much smaller amounts recovered in the faeces. The major urinary excretion products in man are milrinone (83%) and its o-glucuronide metabolite (12%).

### **Elimination**

Elimination in normal subjects via the urine is rapid, with approximately 60% recovered within the first two hours following dosing and approximately 90% recovered within the first eight hours following dosing. The mean renal clearance of PRIMACOR is approximately 0.3 litres/min while that of the metabolites is even greater, indicative of active secretion.

## **5.3 PRECLINICAL SAFETY DATA**

### **Carcinogenicity / Mutagenicity**

Twenty-four months of oral administration of PRIMACOR to mice at doses up to 40 mg/kg/day was unassociated with evidence of carcinogenic potential. Neither was there evidence of carcinogenic potential when PRIMACOR was orally administered to rats at doses up to 5 mg/kg/day for 24 months or at 25 mg/kg/day for up to 18 months in males and 20 months in females.

Whereas the Chinese Hamster Ovary Chromosome Aberration Assay was positive in the presence of a metabolic activation system, results from the Ames Test, the Mouse Lymphoma Assay, the Micronucleus Test and the *in vivo* Rat Bone Marrow Metaphase Analysis indicated an absence of mutagenic potential.

### **Animal Toxicity**

Oral and intravenous administration of toxic dosages of PRIMACOR to rats and dogs resulted in myocardial degeneration/fibrosis and endocardial haemorrhage, principally affecting the left ventricular papillary muscles. Coronary vascular lesions characterised by periarterial oedema and inflammation have been observed in dogs only. The myocardial/endocardial changes are similar to those produced by  $\beta$ -adrenergic receptor agonists such as isoprenaline, while the vascular changes are similar to those produced by minoxidil and hydralazine.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Glucose

Lactic acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

### **6.2 INCOMPATIBILITIES**

There is an immediate chemical interaction which is evidenced by the formation of a precipitate when frusemide is injected into an intravenous line of an infusion of PRIMACOR. Therefore frusemide or bumetanide should not be administered in intravenous lines containing PRIMACOR.

PRIMACOR should not be diluted in sodium bicarbonate intravenous solution.

### **6.3 SHELF LIFE**

3 years

Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbiological hazards. Preparations not used within 24 hours should be discarded.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30°C. Avoid freezing.

For storage conditions after dilution of the medicine, see section 6.3.

## **6.5 NATURE AND CONTENTS OF CONTAINER**

Glass ampoules containing 10 mL in a pack of 10.

## **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**

0.45% saline, 0.9% saline and 5% glucose may be used as diluents.

100 micrograms/mL: Prepare by adding 90 mL diluent per 10 mg ampoule (10 mL) PRIMACOR.

150 micrograms/mL: Prepare by adding 57 mL diluent per 10 mg ampoule (10 mL) PRIMACOR.

200 micrograms/mL: Prepare by adding 40 mL diluent per 10 mg ampoule (10 mL) PRIMACOR.

Note: Intravenous drug products should be inspected visually and should not be used if particulate matter or discolouration is present.

## **7 MEDICINE SCHEDULE**

Prescription Medicine

## **8 SPONSOR**

sanofi-aventis new zealand limited  
Level 8, 56 Cawley Street  
Ellerslie  
Auckland  
New Zealand  
Toll Free Number (medical information): 0800 283 684  
Email: medinfo.australia@sanofi.com

## **9 DATE OF FIRST APPROVAL**

08 September 1988

## **10 DATE OF REVISION OF THE TEXT**

18 September 2018

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<b>Section changed</b>	<b>Summary of new information</b>
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All	Align with the Medsafe data sheet format including minor additions of text to meet requirements.
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