PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

MILRINONE 1 mg/ml, solution for injection/infusion

MACURE PHARMA ApS

DLP: 31-DEC-2016 Version: 2.0

VI.2. Elements for a Public Summary

VI.2.1. Overview of disease epidemiology

Congestive heart failure (CHF)

Heart failure is a major public health issue, with a prevalence of over 23 million worldwide. This syndrome affects more men than women and its prevalence and incidence greatly increase with advancing age. In the USA, black individuals tend to have a higher prevalence of heart failure and present with heart failure at a younger age than those who are white.

Risk factors include family history, high blood pressure, diabetes, drinking too much alcohol, smoking, obesity, lack of physical activity, unhealthy diet and stress.

CHF is generally a progressive disease with periods of stability punctuated by episodic clinical exacerbations. The course of the disease in any given individual, however, is extremely variable. After the diagnosis of heart failure, survival estimates are 50% and 10% at 5 and 10 years, respectively. Disparities may also exist among racial or ethnic divisions: mortality in black individuals is consistently higher than in white patients.

Acute heart failure in children

Acute heart failure is the rapid development or change of signs and symptoms of heart failure that requires medical attention and usually leads to patient hospitalization and represents a major public health issue. In children, cardiac failure is most often caused by congenital heart disease and cardiomyopathy. These causes are significantly different from those usually responsible for the condition in adults, which include coronary artery disease and high blood pressure. In the United States, there are roughly 14,000 hospitalizations annually which approximates to eighteen admissions per 100,000 children.

There are many patients at risk for heart failure from a number of disorders, including congenital heart disease, myocarditis, cardiomyopathy, metabolic disorders, and effects of medications (e.g.,

anthracyclines).

Hospital mortality in children with heart failure ranged from 4.7% for children with congenital heart disease to 25.0% for cardiomyopathies.

VI.2.2. Summary of treatment benefits

In adults, milrinone is indicated for the short-term treatment (48 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy. 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 and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.

Milrinone works to increase the heart's contractility. It is also a vasodilator that works by relaxing the muscles in your blood vessels to help them dilate (widen). This lowers blood pressure and allows blood to flow more easily through your veins and arteries.

VI.2.3. Unknowns relating to treatment benefits

Insufficient data is available regarding the use of the product during pregnancy and lactation. According to the reference safety information, milrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. In breast-feeding women, 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 for the woman.

VI.2.4. Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Immediate use in patients following an acute heart attack (myocardial infarction).	Use of milrinone in the acute phase after a heart attack may lead to an undesirable increase in myocardial oxygen consumption.	Yes, by closely monitoring of patients.
Use in severe narrowing of the heart valves (obstructive aortic or pulmonary valve disease) or narrowing at aortic subvalvar level that leads to obstruction	Milrinone may aggravate outflow obstruction in these conditions.	Yes, by closely monitoring of patients.

(hypertrophic subaortic stenosis)		
Certain types of heart rhythm disorders originating from the upper chamber (auricle) or lower chamber (ventricle) of the heart in high-risk populations (supraventricular and ventricular arrhythmias in high-risk populations)	Milrinone may promote certain hearth rhythm disorders originating from the upper chamber or lower chamber of the heart in high-risk population.	Yes, by closely monitoring of patients.
Use in patients with certain forms of heart rhythm disorders (e.g., uncontrolled atrial flutter/fibrillation)	There is a possibility of an increased ventricular response rate in patients with atrial flutter or fibrillation.	Yes, by closely monitoring of patients.
Severe, as-yet untreated dehydration (hypovolaemia)	Milrinone should not be used in patients suffering from severe, as-yet untreated dehydration.	Yes, by closely monitoring of patients.
Low serum potassium levels (Hypokalaemia)	Potassium loss due to excessive diuresis may predispose digitalised patients to heart rhythm disorders.	Yes, by closely monitoring of patients.
Concomitant intravenous administration of diuretics (furosemide and bumetanide) in same IV line as Milrinone	Taking water tablets (diuretics) at the same time as milrinone may enhance their effect in terms of increasing urine output and lowering potassium.	Yes, by closely monitoring of patients.
Allergy (hypersensitive) to milrinone (active substance) or any of the other ingredients of Milrinone	Milrinone should not be used in patients who are allergic to milrinone or any of the other ingredients of Milrinone Carino.	Yes, by closely monitoring of patients.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Reduced number of blood platelets (thrombocytopenia) in neonatal patients with risk factors for intraventricular haemorrhage	In neonates with risk factors of intraventricular haemorrhage (i.e., preterm infant, low birth weight), milrinone may induce a blood disorder in which there are too few platelets in the blood.
Slowing the closure of the ductus arteriosus in paediatric population. Ductus arteriosus is a connection between 2 major blood vessels (aorta and pulmonary artery)	In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in paediatric population.
Use in patients suffering from kidney disorder, with dose adjustment	Dosage adjustment in patients suffering from kidney disorder is required.

Missing information	
Risk	**What is known**
Use in paediatric patients with renal impairment	There is limited information regarding the use of the product in this population. The use of milrinone is not recommended in this population.
Use during pregnancy and lactating patients	There is limited information regarding the use of the product in this population: - Milrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. - A decision must be made whether to discontinue breast-feeding or to discontinue Milrinone Carino therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Infusions for periods exceeding 48 hours in adults and infusions for periods exceeding 35 hours in children.	There is no experience in controlled trials with infusions of this product exceeding 48 hours.

VI.2.5. Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6. Planned post authorisation development plan

Not applicable.

VI.2.7. Summary of changes to the Risk Management Plan over time

Not applicable.