IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Milrinone 1 mg/ml Solution for Injection/Infusion
Milrinone
PA0281/244/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6118/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on10/01/2019 under procedure number IE/H/0620/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/244/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Milrinone 1mg/ml Solution for injection/infusion (PL 29831/0619; UK/H/6118/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Ireland and Malta as Concerned Member States (CMS).

This product is a Prescription Only Medicine (legal classification POM).

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The reference product is Primacor 1mg/ml Solution for Injection (PL 04425/0646; Aventis Pharma Limited), which was granted a licence in the UK on 15 July 2010. This followed a change of ownership from Primacor Injection (PL 11723/0064; Sanofi-Synthelabo Limited) which was granted a licence in the UK on 01 May 1994. This, in turn, followed a change of ownership from PL 00071/0323 (Smithkline Beecham SWG Limited), which was granted a licence in the UK in 1989.

Milrinone 1mg/ml Solution for injection/infusion 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 the paediatric population Milrinone 1mg/ml Solution for injection/infusion 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.

This product contains the active ingredient milrinone, which is a phosphodiesterase inhibitor. Milrinone is a positive inotrope and vasodilator, with little chronotropic activity. It also improves left ventricular diastolic relaxation. It differs in structure and mode of action from the digitalis glycosides, catecholamines or angiotensin converting enzyme inhibitors. It is a selective inhibitor of peak III phosphodiesterase isoenzyme in cardiac and vascular muscle. It produces slight enhancement of A-V node conduction, but no other significant electrophysiological effects.

In clinical studies Milrinone Injection 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.

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, a 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.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Milrinone 1mg/ml Solution for injection/infusion is an aqueous solution at the time of administration and in line with the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 24 July 2016. After a subsequent national phase, a licence was granted in the UK on 01 August 2016.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

Milrinone 1mg/ml Solution for injection/infusion is 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. Each 10 ml ampoule of Milrinone 1mg/ml Solution for injection/infusion contains 10 mg milrinone. Each ml of solution contains 1 mg milrinone.

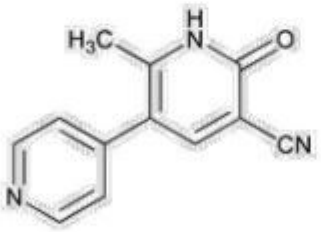
Other ingredients consist of the pharmaceutical excipients, namely (S)-lactic acid, anhydrous glucose, water for injections, sodium hydroxide (for pH adjustment) and lactic acid (for pH adjustment).

The finished product is packaged in 10 ml clear, neutral glass (Type I) ampoules. The ampoules are packed in a polyvinyl chloride tray and cardboard box in packs of 10.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Milrinone
Chemical name(s): 1,6-Dihydro-2-methyl-6-oxo[3,4'-bipyridine]-5-carbonitrile
Structure:



Molecular formula: $C_{12}H_9N_3O$
Molecular weight: 211.22
Appearance: White to off-white crystalline powder
Solubility: Practically insoluble in water and in chloroform, very slightly soluble in methyl alcohol; freely soluble in dimethyl sulfoxide.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance milrinone.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate an aqueous, sterile and pyrogen-free product that could be considered a generic medicinal product of the currently licensed product, Primacor 1mg/ml Solution for Injection (PL 04425/0646; Aventis Pharma Limited).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on two production scale batches of finished product. The results are satisfactory. The Applicant has committed to carry out process validation on a third production scale batch.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 18 months for the unopened product, with the special storage conditions of "Store below 25°C. Do not freeze. Store in the original package".

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Milrinone 1mg/ml Solution for injection/infusion.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of milrinone are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to milrinone is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Milrinone 1mg/ml Solution for injection/infusion.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of milrinone. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

A bioequivalence study was not submitted as the product meets the criteria regarding parenteral solutions specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous solution at the time of administration and contains an active substance in the same concentration as the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Milrinone 1mg/ml Solution for injection/infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Immediate use in patients following acute myocardial infarction	Special warning and precaution in SmPC section 4.4	None
Use in severe obstructive aortic or pulmonary valvular disease or hypertrophic subaortic stenosis	Special warning and precaution in SmPC section 4.4	None
Supraventricular and ventricular arrhythmias in high risk populations	Special warnings and precautions in SmPC section 4.4 Listed in SmPC section 4.8	None
Use in patients with uncontrolled atrial flutter/fibrillation	Special warnings and precautions in SmPC section 4.4	None
Use in patients with severe hypovolaemia	Contraindication in SmPC section 4.3 Special warning and precaution in SmPC section 4.4 'Hypotension' listed in SmPC section 4.8	None
Use in patients with hypokalaemia	Special warnings and precautions in SmPC section 4.4 Text in SmPC section 4.5 'Hypokalaemia' listed in SmPC section 4.8	None
Concomitant intravenous administration of furosemide and bumetanide in same IV line as milrinone	Drug interaction described in SmPC section 4.5	None
Hypersensitivity to milrinone or any of the excipients	Contraindication in SmPC section 4.3 Listed in SmPC section 4.8	None
Thrombocytopenia in neonatal patients with risk factors for intraventricular haemorrhage	Special warnings and precautions in SmPC section 4.4 Listed in SmPC section 4.8	None
Long term use in patients undergoing cardiac surgery	Text in SmPC section 4.2	None
Slowing the closure of the ductus arteriosus in paediatric population	Text in SmPC section 4.2 Special warning and precaution in SmPC section 4.4 Listed in SmPC section 4.8 Text in SmPC section 5.2 Text in SmPC section 5.3	None
Use in renally compromised patients with dose adjustment	Text in SmPC section 4.2 Special warnings and precautions in SmPC section 4.4	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in paediatric patients with renal impairment	Text in SmPC section 4.2 Special warning and precaution in SmPC section 4.4	None
Use in pregnancy and lactating patients	Text in SmPC section 4.6	None
Infusions for periods exceeding 48 hours in adults and infusions for periods exceeding 35 hours in children	Text in SmPC Section 4.1 Text in SmPC Section 4.2 Special warnings and precautions in SmPC Section 4.4	None

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Milrinone 1mg/ml Solution for injection/infusion.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with milrinone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/6118/1/DC to IE/H/0620/1/DC			
MAH transfer				04/01/2021