CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Milrinon Hikma 1 mg/ml, solution for injection
Hikma Farmaceutica, S.A., Portugal

milrinone lactate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1753/001/MR
Registration number in the Netherlands: RVG 34197

16 August 2010

Pharmacotherapeutic group:	cardiac stimulants excl. cardiac glycosides, phosphodiesterase inhibitors
ATC code:	C01CE02
Route of administration:	intravenous
Therapeutic indication:	short-term treatment (48 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy
Prescription status:	prescription only
Date of first authorisation in NL:	10 December 2008
Concerned Member States:	Mutual recognition procedure with AT and DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Milrinon Hikma 1 mg/ml, solution for injection from Hikma Farmaceutica, S.A. The date of authorisation was on 10 December 2008 in the Netherlands.
The product is indicated for the short-term treatment (48 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotension converting enzyme (ACE) inhibitors).

A comprehensive description of the indications and posology is given in the SPC.

Milrinone is a positively inotropic substance with a direct vasodilatory effect and a slight chronotropic activity. Milrinone is a selective inhibitor of cyclic AMP phosphodiesterase III in cardiac and vascular muscle cells. An increase in cAMP concentrations leads, in the *cardio*myocyte, to increased availability of calcium ions during systole and a more rapid decrease of calcium concentrations during diastole *resulting in increased contractility of cardiac muscle*. In the vascular smooth muscle, it leads to decreased availability of calcium and to relaxation. The susceptibility of myofibrillar proteins to calcium is not increased by milrinone. *In addition to increased contractility of cardiac muscle, milrinone also improves diastolic function (lusitropic effect).* With regard to chemical structure and mechanism of action, milrinone differs from both catecholamines and digitalis glycosides.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Corotrope, solution for injection 1 mg/ml (NL License RVG 12820) which has been registered in the Netherlands by Sanofi-Aventis B.V. since 23 November 1989. In addition, reference is made to Conotrope authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Milrinon Hikma 1 mg/ml is a product for parenteral use in aquous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is milrinone, an established active substance described in the US Pharmacopoeia (USP*). The drug substance is an off-white to tan, hygroscopic, crystalline powder, practically insoluble in water, in alcohol and in ether. It sparely dissolves in dilute solutions of mineral acids, is freely soluble in dimethyl sulfoxide, and dissolves in dilute solutions of alkali hydroxides and sodium hydrosulfite. Milrinone exhibits no chirality, XRD analysis has revealed that consistently the same polymorphic form is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing of Milrinone is an entirely chemical synthesis process. The process consists of four stages. The manufacturing process has been sufficiently validated. In general sufficient information has been provided on the synthesis. Also for the starting materials and solvents acceptable specifications have been adopted. The drug substance has been adequately characterized.

Quality control of drug substance
The drug substance specification is in line with the USP monograph for milrinone, with additional requirements for residual solvents, bacterial endotoxins and microbiological quality. The specification for the only degradant and for the unkown impurities, are set in conformity with ICH Guidelines. The specification in general is acceptable in view of the route of synthesis and the various ICH Guidelines. The MAH submitted batch analysis results of two batches, demonstrating compliance with the specification.

Stability of drug substance
Stability data have been obtained at 25°C/60% RH and 40°C/75% RH. At long term conditions stability data have been submitted of 7 batches covering the whole claimed shelf life of 36 months. The drug substance showed to be stable over this period. The granted storage conditions and shelf-life of the drug substance are 36 months, when stored below 25 ºC.

** USP is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

Medicinal Product

Composition
Milrinon Hikma 1 mg/ml is a sterile, clear and colourless, milrinone lactate solution, equivalent to 1 mg milrinone per ml.

The solution for injection is packed in 10 ml clear, type I glass vials.

The excipients are: DL-lactic acid (E270), glucose, sodium hydroxide (E524) and water for injection.

Pharmaceutical development
Development trials were carried out with the aim of producing a sterile parenteral formulation, consistent with the reference drug product marketed in Europe. The use of the excipients finally chosen is consistent with the formulation of the reference drug product in Europe. The pH of the drug product is in the range 3.2 – 4.0.
Since milrinone injection has historically shown to be a stable drug product not sensitive to heat, the standard overkill autoclaving process is chosen as terminal sterilisation. Besides this, before filling, the bulk solution is submitted to sterilizing filtration to reduce bioburden prior to terminal sterilization.
The possibility of extractables and leachables that might migrate from the rubber stoppers has been studied. Satisfactory results were provided. No overages are used. Each vial is filled with such a volume that the declared amount (10ml) can be extracted from the container, in conformity with the Ph.Eur. test for extractable volume of parenteral preparations. The pharmaceutical development has been sufficiently described.

Manufacturing process
Milrinone is dissolved to form the soluble lactate salt (milrinone lactate). This solution is added to another solution, after which the pH of the solution is adjusted to 3.2 – 4.0. The solution is then filtrated, filled into glass vials and autoclaved. The manufacturing process was validated on three consecutive, production-scale process validation batches. The MAH committed to validate the first batches of a bigger production scale. The validation data should be available for inspection if requested.

Control of excipients
All excipients are controlled in accordance with the European Pharmacopoeia (Ph.Eur.*). These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, extractable volume, colour and clarity, particulate matter, pH, leak test, osmolality, assay, impurities, sterility and endotoxins. Release, stability and end of shelf-life specifications are generally the same. Specifications and testing of the drug product, with accompanying limits, are in conformity with the Ph.Eur. Batch analysis data have been provided of three production-scale batches. The results for these batches were within specifications set.

Compatability/In-use stability
Compatibility studies were performed with different infusion fluids. The diluents tested were the following: 0.9% Sodium Chloride and 5% Dextrose. No tests were performed with 0.45% sodium chloride; the results obtained with sodium chloride solution 0.9% were extrapolated to the 0.45% strength. All diluted solutions were tested immediately after preparation (initially) and after 24h at room temperature. Compatibility was demonstrated. Chemical and physical in-use stability has been demonstrated for 24 hours at ≤ 25 °C. Another SPC' listed diluent, 0.45% sodium chloride was not tested, but can be considered compatible by extrapolation of results obtained with 0.9% sodium chloride.

Stability of drug product
Stability data covering 24 months were provided; the stability studies are intended to last 36 months. At both long term and accelerated conditions all parameters tested remain stable. The stability results show no deviations for the other specifications, both at long-term and accelerated conditions. Based on the stability data provided, the claimed shelf life of 24 months was granted. The product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

**Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the USA.*

II.2 Non clinical aspects

This product is a generic formulation of Corotrope 1 mg/ml, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of milrinone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Milrinone is a well-known active substance with established efficacy and tolerability.

Milrinon Hikma 1 mg/ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Milrinon Hikma 1 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan
Milrinone was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of milrinone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The participants for the readability test recruited either had suffered from a severe congestive heart failure or from a sudden heart failure e.g. decrease in heart function following heart surgery or people who care for those suffering from one of the above mentioned diseases. This group was complemented by people from different age and educational groups.
The pilot test showed that the PIL could be rated as readable and comprehensible, although some difficulties were identified. After the pilot test, some improvements were introduced which address the identified problems. The questionnaire of the pilot test was not changed for the main test.
The PIL achieved an Independent Readability Index of 86.8 in the first cycle. The information to answer some questions was not found by some of the participants. The PIL was revised and to enhance the finding results. Some sentences were rephrased to further improve the comprehensibility. After the implementation of these changes the PIL achieved an Independent Readability Index of 93.6 in the second cycle. In this cycle all questions passed the necessary criteria for the individual Readability of each question except one. A revision was made by introducing a sub heading in the paragraph which addresses a dosage adjustment for the elderly that has to be considered by healthcare specialists

administering the injection. The participants also made useful suggestions and criticism to further improve the PIL. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Milrinon Hikma 1 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Corotrope, solution for injection 1 mg/ml. Corotrope is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other milrinone containing products.

The Board followed the advice of the assessors. Milrinon Hikma 1 mg/ml, solution for injection was authorised in the Netherlands on 10 December 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Milrinon Hikma 1 mg/ml, solution for injection with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 12 January 2010.

A European harmonised birth date has been allocated (16 October 1987) and subsequently the first data lock point for milrinone is October 2012. The first PSUR will cover the period from January 2010 to October 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 June 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to validate the first batches of a bigger scale. The validation data should be available for inspection if requested.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached