CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amiodaron HCl Hikma, 50 mg/ml solution for injection
Hikma Farmaceutica S.A., Portugal

amiodarone hydrochloride

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/1098/001/MR
Registration number in the Netherlands: RVG 32850

27 October 2009

Pharmacotherapeutic group:	antiarrhythmics, class III
ATC code:	C01BD01
Route of administration:	intravenous
Therapeutic indication:	prophylaxis and treatment of serious cardiac arrhythmias, in cases where other therapies are not effective or contraindicated
Prescription status:	prescription only
Date of first authorisation in NL:	10 January 2007
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, IT, PT
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 Amiodaron HCl Hikma, 50 mg/ml solution for injection, from Hikma Farmaceutica S.A.. The date of authorisation was on 10 January 2007 in the Netherlands.

The product is indicated for the prophylaxis and treatment of serious cardiac arrhythmias, in cases where other therapies are not effective or contraindicated:

- atrial arrhythmias, including atrial fibrillation or flutter;
- AV nodal arrhythmias and AV reentrant tachycardia, e.g. as a manifestation of Wolff-Parkinson-White syndrome;
- life-threatening ventricular arrhythmias, including persistent or non-persistent ventricular tachycardia or episodes of ventricular fibrillation.

Amiodaron HCl Hikma is used in patients in whom a rapid response is desired or for whom oral administration is not possible.

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

Amiodarone is a di-iodinated benzofuran derivative and is classified as a class III antiarrhythmic agent owing to its ability to increase the cardiac action potential duration in both atrial and ventricular myocytes via block of cardiac K+ channels (mainly of the rapid component of the delayed rectifier K+ current, IKr). Thus, it prolongs the refractory period of the action potential leading to depression of ectopies and re-entry-arrhythmias and to prolongation of the QTc interval in the ECG. Furthermore, Amiodarone also blocks cardiac Na+ currents (class I effect) and Ca2+ currents (class IV effect). The latter may lead to slowing of conduction through the sinoatrial and atrioventricular nodes.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cordarone I.V. (NL RVG 10937), which has been registered in the Netherlands by Sanofi-Aventis since 1987. In addition, reference is made to Cordarone I.V. 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 Amiodaron HCl Hikma is a product for parenteral use, 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.

No paediatric development programme has been submitted, as this is not required for a generic medicinal product.

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 amiodarone hydrochloride, an established active substance described in the Europea Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white fine crystalline powder, which is very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol, and sparingly soluble in alcohol.

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.

Manufacture
The process has been in use for over 30 years without changes in its fundamental set-up. The synthetic route followed was taken into account when the Ph.Eur. monograph was elaborated. The monograph is suitable to control the purity of the substance. In view of this, no further details on process development were deemed necessary.

Control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for related substances. Batch analytical data demonstrating compliance with this specification have been provided for 5 full-scale batches.

Stability
Stability data on the active substance have been provided for 11 commercial-scale batches stored at 25ºC/60%RH (up to 60 months) and 3 batches stored at 40ºC/75%RH (6 months) in accordance with applicable European guidelines. The batches were adequately stored. Based on the data submitted, a retest period of 5 years could be granted with no specific storage conditions.

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

Medicinal Product

Composition
Amiodaron HCl Hikma contains as active substance 50 mg/ml of amiodarone hydrochloride, and is a clear pale yellow solution with pH 3.7-4.3.

The solution for injection is packed in a clear, colourless glass ampoule packing material of 5 ml, containing 3 ml solution.

The excipients are: polysorbate 80 (E433), benzyl alcohol, water for injection

Pharmaceutical development
The product is identical to the originator product with respect to its composition, excipients and primary packaging. Essential similarity can be safely accepted. Polysorbate is needed to dissolve the amiodarone. Benzyl alcohol also improves the solubility. Its capacities as an antimicrobial preservative are not used in the product; the finished product is sterile and the ampoules are for single use. Nitrogen gas is used during the production process to remove oxygen from the solution. The pharmaceutical development process has been adequately described. The excipients polysorbate 80, benzyl alcohol and water for injections comply to their Ph.Eur. monograph, whereas the USP/NF specifications are used for nitrogen. As the USP/NF specifications for nitrogen gas are less stringent than the Ph.Eur, the MAH committed to change to Ph.Eur. quality nitrogen gas post-approval.

Manufacturing process
The manufacturing process includes de-oxygenation, dissolution and sterile filtering steps. No overages are used in producing the bulk solution. The solution is filled aseptically into the ampoules (with control of the filling volume to assure an acceptable extractable volume), after which the filled ampoules are sealed and tested for leaks. Terminal sterilisation by the standard processes results in unacceptable degradation of amiodarone. This justifies the use of sterile filtration. They are also tested for the absence of sub-visible particles.
Process validation was performed on three pilot-scale stability batches; the first three commercial batches will be used post-approval to validate the process at full scale.

Compatibility with diluents and dosage devices
Only dextrose 5% should be used. The stability of the dextrose dilutions described in the SPC are found of acceptable purity after appropriate "storage" times at room temperature. Another study shows the incompatibility with plastics containing DEHP. Such materials should be avoided in the infusion systems used. This information is included in the SPC.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. No overage is used. The specification includes tests for appearance, identity, colour of solution, iodides, extractable volume, pH, particles, leakage, assay, benzyl alcohol, related substances, sterility, bacterial endotoxins and benzaldehyde. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Validation data of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished product meet the specifications.

Stability tests on the finished product
Stability data were submitted of three batches (50% of full scale) stored at 25ºC/60%RH (24 months) and 40ºC/75%RH (6 months) in accordance with applicable European guidelines. The samples were packaged in the proposed cartons during storage. Based on the data submitted, the proposed shelf-life of 2 years was granted. The labelled storage conditions are: ‘Do not store above 25°C’, ‘Store in the original package in order to protect from light’ and ‘Do not refrigerate or freeze’.
The MAH committed to perform stability tests under intermediate storage conditions and report the results.

In-use stability data showed that the diluted product is physically and chemically stable for 24 hours at room temperature. However, from a microbiological viewpoint, the product should be used immediately after dilution.

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.

II.2 Non clinical aspects

This product is a generic formulation of Cordarone I.V. solution for injection, 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 amiodarone 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

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

Amiodaron HCl Hikma, 50 mg/ml solution for injection is a parenteral aqueous 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 Amiodaron HCl Hikma, 50 mg/ml solution for injection 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
In view of the existing knowledge and experience with the active substance amiodarone, the available data and the known risk benefit profile it is accepted that the MAH will perform the standard pharmacovigilance activities as described in *volume 9 of The rules governing medicinal products in the European Union*.
The safety profile of amiodarone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

Design
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 2 phases: a pilot test and the main test. Firstly a pilot test with 3 participants was performed. The main test consisted of 2 rounds with 10 participants each. The participants either had heart problems, knew someone in their circle of closer acquaintances or family who has taken similar products because of a heart rhythm disorder or were able to imagine a situation in which they would have to use a drug for this indication.
There were sufficient questions about the critical sections. The questions covered the following areas: traceability, comprehensibility and applicability. The test also included open questions regarding the impressions of the participants of the leaflet.
Before the pilot test the leaflet was optimised both with respect to content and liguistically. A pilot test was performed to detect any problems before the main test. As a result the lay-out and wording of some headings were adapted before the main test. With this adapted leaflet the first round of the main test was performed.

Results
More than 90% of the participants were able to locate and understand the information in the leaflet, except for two questions (questions 14 and 16). For question 14 regarding the warning section, it was found that participants experienced difficulties with this question, but 85% of the participants were able to locate the

information and 100% of the participants were able to understand the information. The key words to find the key information has been placed at the beginning of the bullet to aid traceability.
For question 16 regarding the interaction with other medicines, the layout of the section in the leaflet was adapted to improve traceability after the first round, giving the result that all participants were able to locate the information in the second round.

The final conclusion of the test is clear, concise and clearly presented. The member states consider that the patient information leaflet has been adapted sufficiently taking into account the results of the tests.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amiodaron HCl Hikma, 50 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Cordarone I.V., solution for injection. Cordarone I.V. 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 amiodarone containing products.

The Board followed the advice of the assessors. Amiodaron HCl Hikma, 50 mg/ml solution for injection was authorised in the Netherlands on 10 January 2007.

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 Amiodaron HCl Hikma, 50 mg/ml solution for injection with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 4 October 2007.

The PSUR submission cycle is 3 years. The data lock point for the first PSUR will be 10 January 2010, and subsequently the first PSUR will cover the period from October 2007 until January 2010.

The date for the first renewal will be: 10 September 2012.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The USP/NF specifications for nitrogen gas are less stringent than the Ph.Eur. Therefore, the MAH committed to change to Ph.Eur. quality nitrogen gas.
- The MAH committed to provide process validation data of the first three commercial full scale batches.
- The MAH committed to perform stability tests under intermediate storage conditions and report the results.

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
Change in specification of an excipient; addition of a new test parameter to the specification	NL/H/1098/ 001/IB/001	IB	30-9-2008	21-10-2008	Approval	N