COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amiodaron HCl Hameln 20 mg/ml, solution for infusion

(amiodarone hydrochloride)

NL/H/4955/001/DC

Date: 25 February 2021

This module reflects the scientific discussion for the approval of Amiodaron HCl Hameln 20 mg/ml, solution for infusion. The procedure was finalised at 12 November 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amiodaron HCl Hameln 20 mg/ml, solution for infusion, from hameln pharma gmbh.

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

- atrial arrhythmias, including paroxysmal 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

The product can be used where a rapid response is required or where oral administration is not possible. Amiodarone hydrochloride may be used prior to DC cardioversion. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Cordarone I.V. 150 mg/3 ml, solution for injection which has been registered in The Netherlands by Genzyme Europe B.V. since 12 August 1987 via a national procedure.

The concerned member states (CMS) involved in this procedure were Austria, Croatia, Czech Republic, Germany, Hungary, Italy, Slovenia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application. The product applied for differs from the reference product with respect to the strength and pharmaceutical form. It has the same indication, posology and method of administration as the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Amiodaron HCl Hameln is a clear, slightly green-yellow solution free from visible particles. The pH is 2.8 - 3.6 and the osmolality is 270 – 310 mOsmol/kg.

Each ml of solution contains 20 mg amiodarone hydrochloride, equivalent to 18.9 mg amiodarone. Each vial with 50 ml of solution contains 1000 mg amiodarone hydrochloride, equivalent to 946.54 mg amiodarone.

The solution for infusion is packed in 50 ml clear, type II glass vial, closed with bromobutyl rubber stopper and tear-off top cap.

The excipients are: glucose monohydrate, hydrochloric acid (for pH adjustment), polysorbate 80 (E433) and water for injections

II.2 Drug Substance

The active substance is amiodarone hydrochloride, an established active substance described in the European 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 CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The CEP specifications are supplemented with tests for microbial quality and bacterial endotoxins Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Compared to the reference product, Cordarone, the proposed product contains a different strength and no benzyl alcohol. From a quality perspective, no differences are expected in safety and pharmacokinetic profile. A bioequivalence study is not required as the product is to be administered as an aqueous

intravenous solution containing the same active substance, in the same concentration. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

A detailed description of the manufacturing process is provided. Because the drug substance is thermolabile, photo- and oxygen sensitive, an aseptic production process is used and light protection is applied during manufacturing, transport and storage and protection with nitrogen is used during the production. The conditions of depyrogenisation of the glass vials are suitable. Details on the sterilisation of the rubber stoppers are provided. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, (sub) visible particles, extractable volume, osmolarity, pH, light transmission, identification of active substance and dextrose, related substances and iodine, assays for amiodarone HCl and dextrose, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches stored at 5°C (36 months) and 25°C/60% RH (36 months). Results of stability testing, 36 months at 25°C/60% RH and 30°C/75% RH and 6 months at 40°C/75% RH, of the 50 mg/ml concentrate from the same manufacturer have been provided as supportive information. In view of the submitted data, the proposed shelf-life (24 months) and storage condition ("Do not store above 25°C"and "Keep the vials in the outer carton in order to protect from light") are acceptable. After first opening the medicinal product should be used immediately.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amiodaron HCl Hameln has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amiodaron HCl Hameln is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Cordarone which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amiodarone hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Justification for the dosage form

The MAH has formulated a ready to use amiodarone formulation. The reference product of amiodarone solution for injection (Cordarone) is available in concentrated form and needs to be diluted with 5% glucose solution before injection.
The rationale for developing a ready-to-use formulation for amiodarone is accepted. It is expected that a ready-to-use product avoids the risks to patient safety associated with

preparations on the ward. Moreover, it is expected to be available immediately in emergency situations, without a requirement for time-consuming preparation.

IV.3 Pharmacokinetics

The absence of a bioequivalence study can be justified according to Committee for Proprietary Medicinal Products (CPMP) guidelines, the MAH is not required to submit a bioequivalence study if the product is to be administered as an aqueous i.v. solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). Whilst the test product contains the same active substance in an aqueous solution, as the reference product, the concentration of active substance is different. However, manipulation of the infusion rates ultimately means that the test and reference products are infused at the same final dose per unit time. Thus, the absence of a biostudy is accepted. Therefore, clinical efficacy and safety regarding the active substance of the reference product can be extrapolated.

IV.4 Clinical safety

The medicinal product contains polysorbate 80, which is known to cause severe allergic reactions (dyspnoea, swelling, dizziness), and hepatotoxicity (abrupt elevation of liver enzymes). Polysorbates can also cause hemodynamic changes (e.g. hypotension, cardiac depression) and QT prolongation.
The MAH has provided a detailed discussion of differences in content between the proposed medicinal product and the reference product. As the polysorbate content has the same ratio to the active substance as in the reference product, for any given dose, the polysorbate dose is also similar to the reference. Hence, the safety data for the reference product can be extrapolated to the new product, establishing safety.
The major safety issue associated with the administration of high concentrations of intravenous amiodarone is phlebitis. This issue is sufficiently covered. The product must be administered via central venous catheter to mitigate this risk, and a warning is included in the SmPC that patients must be monitored for the occurrence of phlebitis.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, 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 Amiodaron HCl Hameln.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Thyroid disorders • Hepatotoxicity • Pulmonary toxicity • Conduction disturbances • Proarrhythmic disorder (including arrhythmia,

	torsade de pointes and cardiac arrest) • Muscular toxicity in combination with statins • Severe skin reactions (including SJS and TEN)
Important potential risks	• Medication errors
Missing information	• Use in paediatric population

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cordarone. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH confirms that the Patient Information Leaflet for Amiodaron Hameln 20 mg/ml, solution for infusion, is identical to the Patient Leaflet (PL) for hameln pharma plus gmbh Amiodarone hydrochloride 50 mg/ml solution for injection in terms of the layout, design and content, with minor differences relating to the concentration and presentation only. The MAH attached the results of a successful readability test for hameln pharma plus gmbh Amiodarone hydrochloride 50 mg/ml solution for injection and therefore confirms that no separate user testing or bridging study is required in respect of the proposed product.
The final report of the readability test for Amiodarone hydrochloride 50 mg/ml solution for injection has been provided. This report is assessed and approved within procedure DE/H/1898/001/DC.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amiodaron HCl Hameln 20 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Cordarone I.V. 150 mg/3 ml, solution for injection. Cordarone 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. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amiodaron HCl Hameln with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 November 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse