COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Lidocaine Hydrochloride Renaudin 20 mg/ml, solution for injection/infusion

# (lidocaine hydrochloride)

# NL/H/4574/001/DC

# Date: 15 September 2020

**This module reflects the scientific discussion for the approval of Lidocaine Hydrochloride Renaudin 20 mg/ml, solution for injection/infusion. The procedure was finalised at 27 February 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 Lidocaine Hydrochloride Renaudin 20 mg/ml, solution for injection/infusion, from Laboratoire Renaudin.

The product is indicated for:
For cardiology:
Recurrent sustained ventricular tachycardia or tachyarrhythmia not responding to beta-blockers or amiodarone or in the case of contraindications to amiodarone, if related to acute coronary syndromes

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 European Reference Product (ERP) Xylocard 20 mg/ml intraveineux, solution for injection which has been registered in France by Aspen Pharma Trading Ltd since 20 June 1986. In the Netherlands, Xylocard has been withdrawn since 31 December 2001 for commercial reasons.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as an additional indication was requested.

Indications
Initially, the MAH was seeking approval of Lidocaine Hydrochloride Renaudin for additional indications, namely:
*For adults only*

- *For peri-operative analgesia in the context of multimodal analgesia, to reduce postoperative pain and consumption of opioids*
- *For management of refractory pain after failure to previous first-line of opioids or other adjuvant analgesics (i.e. antidepressants, anticonvulsants, ketamine).*

During the application procedure, these indications have been withdrawn.

# II. QUALITY ASPECTS

## II.1 Introduction

Lidocaine Hydrochloride Renaudin is a clear and colourless solution for injection with a pH between 6.0- 7.0 and osmolality ranges between 310 – 350 mOsm/kg. Each ml contains lidocaine hydrochloride monohydrate equivalent to 20 mg of anhydrous lidocaine hydrochloride.

The solution for injection is packed in colourless glass vial of 50 mL closed by a butyl rubber stopper capped with an aluminium cap wearing a purple plastic flip off.

The excipients are: sodium chloride, sodium hydroxide and water for injections.

## II.2 Drug Substance

The active substance is lidocaine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Lidocaine is a white or almost white, crystalline powder. It is very soluble in water and freely soluble in ethanol (96 per cent).

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 and meets the requirements of the monograph in the Ph.Eur. with additional tests for residual solvents and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for six 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. All excipients used are well known in the pharmaceutical industry and are commonly used for this dosage form. The sterilisation process selected, is the preferred type of sterilisation. The time, temperature and pressure of the sterilisation cycle and the bioburden limits before steam sterilisation are specified and

are in line with the requirements of the European Pharmacopoeia and guidelines. Compatibility of the drug product with the container closure system has been demonstrated.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The conditions of the sterilisation cycle are in line with the Ph. Eur. requirements. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with their corresponding pharmacopoeial monographs. These specifications are acceptable.

Microbiological attributes

It is ensured that the drug product is in compliance with the sterility test and the bacterial endotoxin test described in the Ph.Eur. Specifications are fixed according to the corresponding Ph.Eur monographs.

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 characteristics, identification, extractable volume, pH of the solution, osmolality, related substances and degradation products, lidocaine content, sterility test, particulate matter 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 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 batches stored at 25°C/40% RH (36 months), 30°C/65%RH (36 months), 40°C/≤25%RH (6 months), 5°C (vials in upright position; 6 months). All stability results were within acceptance limits and no negative trends were observed. A photostability study showed that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months without special storage conditions. In-use stability studies in order to demonstrate physical and chemical in-use stability at 2°C to 8°C for up to 24 hours, have been carried out.

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 Lidocaine Hydrochloride Renaudin 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 Lidocaine Hydrochloride Renaudin 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 Xylocard 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

Lidocaine 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 Pharmacokinetics

Lidocaine Hydrochloride Renaudin 20 mg/ml, solution for injection/infusion 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

Lidocaine Hydrochloride Renaudin 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.

## IV.3 Clinical efficacy and safety

Ventricular arrhythmia

Originally, the MAH requested a cardiologic indication for "Treatment and prevention of recurrence of life-threatening ventricular arrhythmias, especially in the acute phase of myocardial infarction". Based on RMS comments, this was updated to:

*"For cardiology:*

- *Recurrent sustained ventricular tachycardia or tachyarrhythmia not responding to beta-blockers or amiodarone or in the case of contraindications to amiodarone, if related to acute coronary syndromes"*

This is consistent with the RMS suggestion in the previous round, in line with the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

The MAH has supplied an up to date clinical overview on the use of lidocaine in the management of ventricular arrhythmias, supported by current literature. The data clearly show that prophylactic use of lidocaine for prevention of arrhythmia is not appropriate. However, for therapeutic use (especially 'last resort' use) there is a place, as evidenced by the studies and recognised in the ESC guideline.

Postoperative pain

The indication "*prevention of postoperative pain*" was not supported. Efficacy had not been robustly shown and was inconsistent over surgical settings and treatment centres. The indication needed to be further justified. The clinical relevance of the short-term analgesic effects after lidocaine infusion also needed to be further substantiated via secondary endpoints, e.g. reduction in use of opioids and rescue medication, faster recovery, reduction in hospital stay etc. Extrapolation from the non-European studies to the EU target population was not satisfactorily justified. In absence of additional supporting data, the MAH withdrew the indication "prevention of postoperative pain" for this application.

Refractory/cancer pain

No clear evidence was provided in support of this indication (refractory (neuropathic) pain/ cancer pain), where higher dosages are proposed than for the ventricular arrhythmia indication. The studies in post-operative setting that were available from the literature were often small-scaled and of short duration, and safety data were not systematically reported. The data are insufficient to make the benefit-risk balance. Therefore, the indication was withdrawn before finalisation.

### IV.4 Risk Management Plan

The MAH 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 Lidocaine Hydrochloride Renaudin.

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

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | - Medication errors |
| Missing information | - Use in paediatric population<br>- Use during pregnancy |

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

### IV.5 Discussion on the clinical aspects

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

## V. USER CONSULTATION

The package leaflet (PL) 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 2 participants followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lidocaine Hydrochloride Renaudin 20 mg/ml, solution for injection/infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Xylocard 20 mg/ml intraveineux, solution for injection. Xylocard 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 was deemed necessary. A biowaiver has been granted.

In the Board meeting of 5 December 2018, the requested indications were discussed. After adjustment of the cardiologic indication and removal of the analgesic indications the Board agreed with approval of product Lidocaine Hydrochloride Renaudin.

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 Lidocaine Hydrochloride Renaudin with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 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 |
|---|---|---|---|---|---|
| NL/H/4574/001 /II/001 | Variation type II C.I.6.a) Addition of new therapeutic indication | Yes | On going | NA | NA |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |