IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lidocaine hydrochloride Noridem 10 mg / mL (1 % w/v) solution for injection
Lidocaine Hydrochloride Monohydrate
Anhydrous Lidocaine Hydrochloride
PA1122/027/001

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Lidocaine hydrochloride *Noridem 10 mg/mL (1% w/v) Solution for Injection*, from Noridem Enterprises Limited on 19th November 2021 for

- Local and regional anaesthesia: lidocaine hydrochloride Noridem 10 mg/mL (1% w/v) is indicated in adults, adolescents and children over 2 years of age. In children under 2 years only limited data are available.

This decentralised application concerns a generic version of Lidocaine hydrochloride monohydrate, solution for injection containing 10 mg/mL (1% w/v) lidocaine hydrochloride.

The originator product is 1% w/v Lidocaine Hydrochloride Injection BP (strengths, pharmaceutical form) by B. Braun Medical Limited, registered in Ireland since 22/4/1992.

The product will be available on prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at WWW.HPRA.IE

Name of the product	Lidocaine hydrochloride Noridem 10 mg/ml (1% w/v) solution for injection
Name(s) of the active substance(s) (INN)	Lidocaine hydrochloride
Pharmacotherapeutic classification (ATC code)	N01BB02
Pharmaceutical form and strength(s)	1% solution for injection
Marketing Authorisation Number(s) in Ireland (PA)	PA1122/027/001
Marketing Authorisation Holder	Noridem Enterprises Limited
MRP/DCP No.	IE/H/1089/001/E/001
Reference Member State	IE
Concerned Member State	AT CZ DK ES FI HU IT NL NO PT RO SE SK

II. QUALITY ASPECTS

This application is for Lidocaine Hydrochloride Noridem 10 mg/mL (1 % w/v) Solution for Injection

II.2 Drug substance

The active substance is Lidocaine Hydrochloride (as Lidocaine Hydrochloride Monohydrate), an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

The excipients in the medicinal product are listed in section 6.1 of the SmPC.

A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring the consistent quality of Lidocaine Hydrochloride Noridem 10 mg/mL (1% w/v) Solution for Injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Lidocaine Hydrochloride Injection BP 1% w/v on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/a

III.5 Ecotoxicity/environmental risk assessment

Since Lidocaine hydrochloride is a generic product, it will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Lidocaine Hydrochloride are well known. As Lidocaine Hydrochloride is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Nonclinical section of the SmPC are in line with the originator which is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lidocaine hydrochloride Noridem 10 mg / mL (1 % w/v) solution for injection is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product 1% w/v Lidocaine Hydrochloride Injection BP (strengths, pharmaceutical form) by B. Braun Medical Limited, registered in Ireland since 22/4/1992.

There were no Bioequivalence studies conducted in support of this application. **Lidocaine/Noriderm** is a parenteral solution which contains the same active substance and excipients in the same concentration as the reference medicinal product and in accordance with the Guideline on the investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1. no bioequivalence study is required.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product marketed by MAH.

IV.2 Pharmacokinetics

Absorption
Plasma levels depend on the site and mode of administration. However, there is a poor relationship between the amount of local anaesthetic injected and peak plasma levels. After intravenous administration the bio-availability is 100 %. Maximum concentrations are achieved within latest 30 minutes, in the majority of patients maximum concentrations are met within 10 – 20 minutes.

After ***intramuscular injection*** of 400 mg of lidocaine Hydrochloride monohydrate for intercostal block the maximum plasma concentration (Cmax) has been determined to be 6.48 mg/L, attained after 5 – 15 min (tmax).
After ***intravenous administration***, onset of the therapeutic effect of lidocaine is rapid. Therapeutic plasma concentrations are reached within 1 – 2 min. The effect of a bolus injection lasts for 10 – 20 min; in order to maintain the therapeutic effect of lidocaine, its administration must be continued in the form of an intravenous infusion.
After ***continuous infusion*** and when no loading dose is given the steady state of plasma concentration was achieved not earlier than 5 hours (range, 5 – 10 hours) of beginning of the infusion. However, therapeutic concentrations had already been achieved after 30 – 60 min.
After ***subcutaneous administration***, Cmax values reached 4.91 mg / L (vaginal injection) or 1.95 mg / L (abdominal injection), respectively. In a study involving 5 healthy volunteers, after maxillar-buccal infiltration anaesthesia with 36 mg of lidocaine, using a 2 % solution, the Cmax value reached 0.31 mg / L.
After ***epidural injection*** the measured maximum plasma concentrations do not seem to be directly proportional to the dose applied. Administration of 400 mg resulted in Cmax values of 3 – 4 mg / L. No data are available on pharmacokinetics after intrathecal administration.

Distribution
Lidocaine follows a biphasic elimination kinetic. After intravenous administration the drug substance is first rapidly distributed from the central compartment into intensively perfused tissues and organs (α-distribution phase). This phase is followed by redistribution into skeletal muscles and adipose tissue. The half life time during the α-distribution phase is approximately 4 – 8 minutes. Distribution into peripheral tissues is predicted to occur within 15 min. The plasma protein binding rate is approximately 60 – 80 per cent in adults. It is dependant on the drug concentration and additionally on the concentration of the α-1-acid glycoprotein (AAG). The AAG is an acute phase protein that is binding free
lidocaine and may be increased e.g. after trauma, surgery or burns depending on the pathophysiological condition of the patient. To the contrary it had been shown that AAG concentrations are low in neonates and patients suffering from liver impairment leading to a marked reduction of lidocaine plasma protein binding.
The distribution volume may be altered in patients suffering from further diseases, e.g. heart insufficiency, liver insufficiency or renal insufficiency.

Biotransformation
Besides distribution of Lidocaine in other compartments (e.g. cerebrospinal fluid), the drug is rapidly metabolised in the liver by mono-oxygenases mainly via oxidative desalkylation, hydroxylation at the aromatic ring and hydrolysis of the amide bond. Hydroxylated derivatives undergo conjugation. In total, approx. 90 % of lidocaine is metabolised to 4- hydroxy-2,6-xylidine, to 4-hydroxy-2,6-xylidine glucuronide and to a lower degree to the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX). The two latter may accumulate during infusions of longer duration or in the presence of renal insufficiency due to their longer half life time as compared to lidocaine itself. In liver diseases the metabolic rate may be reduced to 10 – 50 per cent of normal.
Results with human liver microsomes and recombinant human CYP isoforms demonstrated that CYP1A2 and CYP3A4 enzymes are the major CYP isoforms involved in lidocaine N-deethylation.
The hepatic blood flow appears to limit the rate of lidocaine metabolism. As a consequence the plasma *t1/2* of lidocaine and its metabolites may be prolonged and significant effects on pharmacokinetics and dosage requirements of lidocaine are to be expected in patients with impaired liver perfusion, e.g. after acute myocardial infarction, in the presence of cardiac insufficiency, liver disease or congestive heart failure.

Elimination
Less than 10 per cent of lidocaine is excreted unchanged in urine, the remaining proportion in the form of the metabolites.
The elimination half-life time is 1.5 – 2 hours in adults and approx. 3 hours in new-borns.
The half-life times of the active metabolites monoethyl glycine xylidide (MEGX) and glycine xylidide (GX) are 2 – 6 hours and 10 hours, respectively. Since their plasma *t1/2* are longer than that of lidocaine, accumulation of metabolites, particularly GX, may occur during prolonged infusion. Additionally, the elimination rate depends on the pH; it can be increased by acidification of the urine. The plasma clearance is about 0.95 mL / min.

Paediatric population
After epidural anaesthesia of the mother, the elimination half-life time in the new-born was approximately 3 hours; after infiltration of the perineum and after paracervical block lidocaine was found in the urine of the new-born during 48 hours following anaesthesia.
The plasma *t1/2* is increased 2 – 3 fold in neonates, due to a slower rate of metabolism and in parts to the expanded distribution volume. Absorption and elimination may be faster in children than adults, although other studies suggested that differences in pharmacokinetics (between children and adults) decrease by correcting for BW.
Pharmacokinetics in special clinical situations
Renal impairment
• In the presence of ***renal insufficiency*** the plasma half-life time of lidocaine seemed to be unaltered except for some accumulation of GX during infusion of 12 hours or more. This accumulation seemed to be associated with long-term administration of the drug. However in patients with severe renal insufficiency clearance of lidocaine was approximately halved and half-life time of lidocaine was about twice the amount than in healthy patients. Elimination half-life and volume of distribution may appear to be prolonged resp. increased in ***the elderly*** due to reduced cardiac output and/or hepatic blood flow.

Pregnancy and lactation
Lidocaine passes across the placental barrier by simple diffusion and reaches the foetus within a few minutes of administration. After epidural administration, the foetal to maternal plasma concentration ratio is 0.5 – 0.7.
After infiltration of the perineum and after paracervical block, markedly higher concentrations of lidocaine have been found in umbilical blood.

The foetus is able to metabolise lidocaine. The levels in foetal blood are approximately 60 % of the concentrations in the maternal blood. Due to a lower plasma protein binding in foetal blood, the concentration of the pharmacologically active free lidocaine is 1.4 fold the maternal concentration. Lidocaine is secreted into breast milk only in small amounts.

IV.3 Pharmacodynamics

Mechanism of action
Local and regional anaesthesia
Lidocaine is a local anaesthetic agent of the amide type.
Lidocaine reduces the permeability of cell membranes for cations, in particular sodium ions, at higher concentrations also for potassium ions. This leads, depending on the concentration of lidocaine, to reduced excitability of the nerve fibres because the increase of sodium permeability producing the action potential is slowed down. From inside the cell the lidocaine molecule enters the open sodium channel and blocks it by binding to a specific receptor. A direct effect of incorporation of lidocaine in the cell membrane is much less relevant.
Because lidocaine, before reaching its site of action, must pass into the cell, its effect depends on its pKa and on the environmental pH, i.e. on the proportion of the free base which is the moiety predominantly migrating through the lipophilic membranes of nerve fibres.
In inflamed tissue the local anaesthetic effect is reduced due to the lower pH in such regions.

Local and regional anaesthesia
Lidocaine inhibits the function of excitable structures such as sensor, motor and autonomic nerve fibres and the cardiac impulse conducting system. Lidocaine reversibly inhibits the conduction in sensitive nerve fibres in the area of application. The order of loss of nerve function is as follows: pain, temperature, touch, and pressure. The local anaesthetic effect of lidocaine lasts for about 30 minutes – 3 hours depending on the type of anasesthesia.
Other pharmacological effects
Lidocaine shows weak parasympatholytic activity. Intradermally administered lidocaine acts at low concentrations as a mild vasoconstrictor and at higher concentrations as vasodilator.
Paediatric population
There are no data indicating that the pharmacodynamic properties of lidocaine in children should be different from those established for adults.

IV.4 Clinical Efficacy

As this is a generic intravenous product with the same qualitative and quantitative composition of the originator as the originator product, there was no safety and efficacy data submitted in report of the application.

IV.5 Clinical Safety

As this is a generic intravenous product with the same qualitative and quantitative composition of the originator as the originator product, there was no safety and efficacy data submitted in report of the application.

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 Lidocaine hydrochloride.

Safety specification

Summary of Safety Concerns	
Important identified risks	Central nervous system toxicity Cardiac toxicity
Important potential risks	None
Missing information	Use in children under 2 years of age

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Periodic Safety Update Reports (PSURs) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

V. OVERALL CONCLUSIONS

The original decentralised application concerns a generic version of Lidocaine hydrochloride monohydrate, solution for injection containing 20mg/mL (2% w/v) lidocaine hydrochloride, with concerned member states Poland and UK(NI).

The originator/reference medicinal product is 1% w/v Lidocaine Hydrochloride Injection BP (strengths, pharmaceutical form) by B. Braun Medical Limited, registered since 22/4/1992.

With Ireland as the Reference Member State in the subsequent repeat use procedure IE/H/1089/001-002/E/001 Noridem Enterprises Limited is applying for the Marketing Authorisations for Lidocaine/DEMO in the member states Austria, Czechia, Denmark, Spain, Finland, Hungary, Italy, Netherlands, Norway, Portugal, Romania, Sweden and Slovakia.

There were no Bioequivalence studies conducted in support of this application. **Lidocaine/DEMO**is a parenteral solution which contains the same active substance and excipient in the same concentration as the reference medicinal product. In accordance with Article 10.1 of Directive 2001/83/EC, the Applicant has submitted a justification why Bioequivalence studies were not performed with respect to Note for Guidance CPMP/EWP/QWP/ 1401/98 Rev 1) and has submitted an update of published literature relevant to the substance and the present application. This is acceptable.

The product information i.e. SmPC & PIL product information leaflet are in line with the reference products-
1% w/v Lidocaine Hydrochloride Injection BP- PA0179/037/001.

VI. REVISION DATE

14.04.2026