LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bupivacaine Noridem
(bupivacaine hydrochloride monohydrate)

SE/H/2059/01-02/DC
2019-1496, 2019-1497

This module reflects the scientific discussion for the approval of Bupivacaine Noridem. The procedure was finalised on 2020-12-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Bupivacaine Noridem, 2.5 mg/ml and 5 mg/ml, solution for injection, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Noridem Enterprises Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CY, CZ, DK, EL, FR, IE, NO, PL, SK and UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Marcain, 2.5 mg/ml and 5 mg/ml, solution for injection authorised in SE since 1972, with Aspen Pharma Trading Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS CY, CZ (2.5 mg/ml only), EL, FR and PL: Marcain, 2.5 mg/ml and 5 mg/ml, solution for injection authorised in SE since 1972, with Aspen Pharma Trading Limited as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during validation period.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physio-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applicant did not submit any bioequivalence study as the applied product is aqueous parenteral solution in which bioequivalence study is not required.

Pharmacokinetic properties of the active substance
Absorption: The absorption rate of bupivacaine depends upon the dose, the route of administration and the vascularity of the injection site.

Elimination: Bupivacaine has a total plasma clearance of 0.58 l/min, a volume of distribution at steady state of 73 l, a terminal half-life of 2.7 h and an intermediate hepatic extraction ratio of 0.40. Half life during elimination in newborns is up to 8 hours longer than in adults. The half life in children above 3 months of age corresponds to the half life in adults.

IV.2 Discussion on the clinical aspects

The applied product is to be administered as a solution for injection containing the same active substance in the same concentration as the currently authorised product. The applied product also contains the same excipients in similar amounts as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

With regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Bupivacaine Noridem.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

RMS comment: The Applicant have justified that all other safety concerns can be removed, there are no safety concerns included in the list of safety concerns as published on the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) website. For bupivacaine hydrochloride, additional risk minimization measures, additional pharmacovigilance activities or targeted questionnaires have not been identified. Routine pharmacovigilance activities and routine risk minimization measures are considered sufficient for the current generic product.
Based on all of the above, the Applicant recommended an empty list of safety concerns to be included in this RMP.

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.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 21st July 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet 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

The quality of the generic product, Bupivacaine Noridem, is found adequate. There are no objections to approval of Bupivacaine Noridem from a non-clinical and clinical point of view. The product information is acceptable.

The benefit/risk ratio is considered positive and Bupivacaine Noridem, 2.5 mg/ml and 5 mg/ml, solution for injection is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bupivacaine Noridem, 2.5 mg/ml and 5 mg/ml, solution for injection was positively finalised on 2020-12-16.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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