LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bupivacaine Spinal Tung Grindeks (bupivacaine hydrochloride monohydrate)

SE/H/2190/01/DC

This module reflects the scientific discussion for the approval of Bupivacaine Spinal Tung Grindeks. The procedure was finalised on 2022-10-05. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bupivacaine Spinal Tung Grindeks, 5 mg/ml, Solution for injection.

The active substance is bupivacaine hydrochloride (monohydrate). A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Bupivacaine Grindeks Heavy, 5 mg/ml, solution for injection, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Grindeks AS, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BG, CZ, DE, EE, HU, IT, LT, LV, NL, PL, RO, SI, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Marcain spinal tung, 5 mg/ml, solution for injection, authorised in Sweden since 1983 with Aspen Pharma Trading Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMSs AT and SI: Marcain spinal tung, 5 mg/ml, solution for injection authorised in Sweden since 1983, with Aspen Pharma Trading Limited as marketing authorisation holder. The justification to use this product is based on RMS's own files.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-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

Pharmacodynamic, pharmacokinetic and toxicological properties of bupivacaine hydrochloride are well known. As bupivacaine hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since product name is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary

There are no objections to approval of product name from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

Biowaiver

No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) since the product is an aqueous parenteral solution.

Discussion and overall conclusion

The applied product is to be administered as an intrathecal solution containing the same active substance in the same concentration as the currently authorised product. The applied product also contains comparable 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).

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Spinal Tung Grindeks.

Safety specification

The MAH has submitted the version 1.1 RMP dated 2022-02-14 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	*Systemic toxicity* *CNS and cardiovascular toxicity* *Consequences of accidental intravascular injection* *Neurological damage such as paralysis and motor weakness*
Important potential risks	*None*
Missing information	*None*

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 1.1 signed 2022-02-14 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 a 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 PL was Latvian.

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 Spinal Tung Grindeks, is found adequate. There are no objections to approval of Bupivacaine Spinal Tung Grindeks, from a non-clinical and clinical point

of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Bupivacaine Spinal Tung Grindeks, 5 mg/ml, Solution for injection was positively finalised on 2022-10-05.

LÄKEMEDELSVERKET
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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se