CBG MEB

Public Assessment Report

Scientific discussion

Bupivacaïne Accord 2.5 mg/ml and 5 mg/ml solution for injection

(bupivacaine hydrochloride)

NL/H/3348/001-002/DC

Date: 6 December 2016

This module reflects the scientific discussion for the approval of Bupivacaïne Accord 2.5 mg/ml and 5 mg/ml solution for injection. The procedure was finalised on 10 November 2015. 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 Bupivacaïne Accord 2.5 mg/ml and 5 mg/ml solution for injection, from Accord Healthcare Ltd.

The product is indicated for:
- surgical anaesthesia in adults and children above 12 years of age
- acute pain management in adults, infants and children above 1 year of age

Bupivacaine is used for the production of prolonged local anaesthesia by percutaneous infiltration, intra-articular block, peripheral nerve block(s) and central neural block (caudal or epidural).
Bupivacaine is also used for pain relief during labour.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Marcaine 0.25% and 0.5%, solution for infusion 2.5 mg/ml and 5 mg/ml (NL license RVG 08028-29) which has been registered in The Netherlands by AstraZeneca B.V. since 28 September 1984.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, Lithuania, Malta, Norway, Sweden, Slovenia and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bupivacaïne Accord is a clear, colourless or almost colourless solution. The pH of the solution is 4.0 to 6.5 and the Osmolality of the solution is 270-320 mOsmol/kg H_2O. Each ml Bupivacaïne Accord 2.5 mg/ml solution for injection contains 2.5 mg bupivacaine hydrochloride (as monohydrate). Each ml Bupivacaïne Accord 5 mg/ml solution for injection contains 5 mg bupivacaine hydrochloride (as monohydrate).

The solution for injection is packed in Type I clear glass ampoules and Type I clear vials with rubber stopper and flip-off seal.

The excipients are sodium chloride, water for injections and sodium hydroxide (E524) for pH adjustment

II.2 Drug Substance

The active substance is bupivacaine hydrochloride (as monohydrate), an established active substance described in the European Pharmacopoeia (Ph.Eur.). Bupivacaine hydrochloride is a white or almost white crystalline powder or colourless crystals. The active substance is soluble in water and freely soluble in ethanol (96%). The solubility in aqueous solutions is pH dependent with good solubility in the range 4.5 – 5.6. Bupivacaine hydrochloride is a racemic mixture, and has the monohydrate polymorphic form.

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 requirements for solvents, bacterial endotoxins and microbial examination. Batch analytical data demonstrating compliance with this specification have been provided for two pilot scale and two full scale 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. The development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The proposed formulations for the products comply with the British Pharmacopoeia monograph for bupivacaine injection, and are qualitatively identical to the reference product. Furthermore, the pH of the solution is identical to the pH of the reference product. The development studies focussed on the development of the manufacturing process, like the method of sterilisation, holding studies and the influence of extremes in pH and temperature. The manufacturing process and the packaging are usual and suitable for the product at issue.
A bioequivalence study is not performed, since the drug product is a solution for injection consisting of the same active substance and excipients as the innovator product. This is justified. The products are pharmaceutically equivalent. The pharmaceutical development of the product has been adequately performed.

Microbiological attributes
The product is a sterile product and it is for single parental use; it does not contain any preservative. The sterility of the product at the release and during shelf life means that the chosen container, with appropriate system closure, prevents microbial contamination. The validation of the sterility method and the bacterial endotoxin method were performed in line with the Ph.Eur. The microbiological attributes are adequately controlled.

Manufacturing process
The manufacturing process consist of identification, weighing, sterilisation, preparation in-process control, filtration, filling, labelling and packaging. The solution for injection is prepared by weighing the components and dissolving in water for injections. The pH is measured and if necessary adjusted to final volume with water for injections. The solution is filtered through a filter before filling. After filling the containers are terminally sterilised by moist heat (≥121°C, for ≥15 minutes). The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for two full scale batches of every presentation of every strength (16 batches in total), in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the current edition of the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. includes tests for description, identification, pH, related bases, related substances, assay, extractable volume, osmolality, sterility, bacterial endotoxins and particulate contamination. 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 two full scale batches of every presentation (16 batches in total) from the proposed production site have been provided, demonstrating compliance with the specification.
The release and shelf-life requirements are identical, except for one specified impurity. The proposed specification is not acceptable as the wider limits for this impurity at shelf-life are not supported by the provided batch analyses and stability data. The MAH is requested to tighten the limit for the impurity to the release limits.

Stability of drug product
Stability data on the product has been provided for two full scale batches of every presentation (16 batches in total) stored at 25°C/60% RH (6–18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The product remained stable under all storage conditions. For all parameters no up or downward trends are observed, and all values for the impurities (including total impurities) remained below quantification limit. A photostability study, in line with ICH guideline, showed that the product is not affected by photo degradation. Based on the submitted stability data a shelf-life of 3 years is justified.

After dilution chemical and physical in-use stability has been demonstrated for 7 days at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8°C, unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

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 Bupivacaïne Accord 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 Bupivacaïne Accord is intended for generic 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 generic formulation of Marcaine 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

Bupivacaine hydrochloride (as monohydrate) 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

Bupivacaïne Accord 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Bupivacaïne Accord is essentially 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 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 Bupivacaïne Accord.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Severe hypotension, bradycardia, arrhythmia (leading to cardiac arrest) - Central nervous system toxicity (i.e. convulsion, numbness of the tongue, tremor) - Allergic reactions (anaphylactic shock) and hypersensitivity
Important potential risks	- Off-label use (intravenous regional anaesthesia (Bier's block), use in paracervical block in obstetrics with risk on foetal bradycardia, long-term use) - Cauda Equina Syndrome (CES)
Missing information	- Use in children <1 year of age - Use in children 1 to 12 years of age for intra-articular block and major nerve block - Use in first-trimester (early) pregnant women

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Marcaine. No new clinical studies were conducted. No new clinical studies were conducted. Based on *in vitro* and literature data, the MAH sufficiently justified that the pharmacokinetic profile of the product will be similar to the pharmacokinetic profile of this reference product. The RMP is acceptable. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Marcaine Polyamp Steripack 2.5 mg/ml and 5 mg/ml solution for injection with regard to content and key massages. With regard to overall layout, design and style of writing, the PL has been compared to the PL of Zolendronic Acid Accord 4 mg/5 ml concentrate for solution for infusion by conducting a successful user test. Both PLs are similar in content. Font, font size, headings and subheadings are almost identical. The layout and critical safety

sections are identical. The target populations for both PLs are similar. Overall, the bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bupivacaïne Accord 2.5 mg/ml and 5 mg/ml solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Marcaine 0.25% and 0.5%, solution for infusion 2.5 mg/ml and 5 mg/ml. Marcaine 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.

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 Bupivacaïne Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 November 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached