

Public Assessment Report

Scientific discussion

**Levobupivacaine Molteni 0.625 mg/ml
and 1.25 mg/ml, solution for infusion**

**Levobupivacaine Molteni
2.5 mg/ml, 5 mg/ml and 7.5 mg/ml,
solution for injection/infusion**

(levobupivacaine hydrochloride)

NL/H/3256/001-005/DC

Date: 6 July 2016

This module reflects the scientific discussion for the approval of Levobupivacaine Molteni. The procedure was finalised on 13 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.
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List of abbreviations

ASMF	Active Substance Master File
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 Levobupivacaine Molteni 0.625 mg/ml and 1.25 mg/ml, solution for infusion, and Levobupivacaine Molteni 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion, from L. Molteni & C. dei F.lli Alitti Società de Esercizio S.p.A.

Levobupivacaine Molteni 0.625 mg/ml and 1.25 mg/ml, solution for infusion are indicated for:

Adults

Pain management

Continuous epidural infusion, for the management of post operative pain and labour analgesia.

Levobupivacaine Molteni 2.5 mg/ml and 5 mg/ml solution for injection/infusion are indicated for:

Adults and adolescents (≥ 12 years)

Surgical anaesthesia

Major, e.g. epidural (including for caesarean section), intrathecal, peripheral nerve block.

Minor, e.g. local infiltration, peribulbar block in ophthalmic surgery.

Pain management

Continuous epidural infusion, single or multiple bolus epidural administration for the management of pain especially post-operative pain or labour analgesia.

Children (< 12 years)

- Analgesia (ilioinguinal/iliohypogastric blocks)

Levobupivacaine Molteni 7.5 mg/ml solution for injection/infusion is indicated for:

Adults and adolescents (≥ 12 years)

Surgical anaesthesia

Major, e.g. epidural, intrathecal, peripheral nerve block.

Minor, e.g. local infiltration, peribulbar block in ophthalmic surgery.

Pain management

Continuous epidural infusion, single or multiple bolus epidural administration for the management of pain especially post-operative pain.

Children (< 12 years)

Analgesia (ilioinguinal/iliohypogastric blocks).

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 product Chirocaine:

- *Solution for infusion*
 - o Chirocaine 0.625 mg/ml and 1.25 mg/ml, solution for infusion (Abbott Scandinavia AB) has been registered in Sweden since 15 November 2002.
- *Solution for injection/concentrate for solution for infusion*
 - o Chirocaine 2.5 mg/ml, 5 mg/ml, and 7.5 mg/ml solution for injection/concentrate for solution for infusion (Abbott Scandinavia AB), has been registered in Sweden since 18 December 1998.

The concerned member states (CMS) involved in this procedure were France (only 0.625, 1.25, 2.5 and 5 mg/ml strengths) and Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Levobupivacaine Molteni is a sterile, clear, colourless isotonic solution with a pH between 4.0-6.0. The osmolality is between 267-310 mOsm/kg.

The drug product is packed in transparent polypropylene bags with an aluminium cover for the 0.625 mg/mL and 1.25 mg/mL strengths with a fill volume of 100 ml or 200 ml, and in polypropylene ampoules (10 mL) for the other three strengths. The polypropylene bag contains one admixture port and one administration port.

The solutions contain levobupivacaine as hydrochloride. The labelled dose of levobupivacaine is expressed as base per ml.

The excipients are water for injections, sodium chloride, hydrochloric acid and sodium hydroxide. The latter two may be added for pH correction.

II.2 Drug Substance

The active substance levobupivacaine hydrochloride is well-known but is not described in the European Pharmacopoeia (Ph.Eur.). However, a Ph.Eur. monograph is available for the racemic mixture bupivacaine hydrochloride. It is a white or almost white crystalline powder, which is freely soluble in water, ethanol, methanol and methylene chloride, and slightly soluble in chloroform and acetone. Levobupivacaine is the S-enantiomer of bupivacaine. Polymorphic form A is manufactured and controlled routinely. Particle size distribution and polymorphic form are not considered relevant though given the fact that the drug product is manufactured as a solution.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The synthesis of levobupivacaine hydrochloride consists of four chemical reaction steps followed by a purification step. No class 1 organic solvents are used. The specifications adopted for the starting materials, solvents and reagents are acceptable. The process has been described in sufficient detail in the ASMF.

Quality control of drug substance

The MAH has adopted the drug substance specification from the manufacturer with additional tests for microbial quality and bacterial endotoxins. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for 3 full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No changes are observed in either the long term stability results and the accelerated stability results. In view of the results no special storage conditions are required. Based on the data submitted, a retest period could be granted of 60 months.

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. The test product was compared to the innovator product taken into account aspects as pH and osmolality as well as assay and impurities. Compatibility of the excipients, pH and isotonicity of the drug product are sufficiently discussed. The choice of packaging, manufacturing process and sterilisation method has been justified.

A bioequivalence study is not performed, since the drug product is an aqueous solution for injection/infusion 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.

Manufacturing process

The solution is prepared by mixing the water for injections with the active substance, sodium chloride and hydrochloric acid or sodium hydroxide for pH adjustment between 5.0-6.0 (solution for infusion) or 5.6-5.9 (solution for injection/infusion). Before filling the ampoules or infusion bags the solution is filtered. The closed packagings are terminally sterilised. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two production scaled batches of each strength and each presentation.

Control of excipients

The excipients comply with the Ph.Eur. or in-house specifications. The in-house specifications are acceptable, since they are deduced from existing Ph.Eur. monographs. These specifications are acceptable.

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.

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 aspect of the bag/ampoule, appearance of the solution, pH, identification, assay, impurities, total sub visible particles, extractable volume, osmolality, sterility of test solution and sterility test of surface (ampoule), bacterial endotoxins and water loss (shelf-life). For the ampoule, the release and shelf life requirements for the upper limit for assay are not identical, all other limits are. 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 have been provided on three production scaled batches of the extreme strengths from the proposed production site, demonstrating compliance with the specification.

Stability of drug product

0.625 mg/ml and 1.25 mg/ml solutions for infusion (bags)

Stability data on the product has been provided for 2 full scaled batches of both strengths stored at 25°C/40% RH (36 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Except for a slight increase in pH, the results show no changes in any of the tested parameters at both storage conditions. All results remained well within limits. Based on these results, the product is regarded as stable for a shelf life of 36 months. Results of the photostability studies do not indicate any degradation; photostability of the product is shown. Specific migration studies were performed, showing acceptable results. No storage conditions are required.

2.5 mg/ml, 5 mg/ml and 7.5 mg/ml solutions for injection/infusion (ampoules)

Stability data on the product has been provided for 2 full scaled batches of the 2.5 mg/ml and 7.5 mg/ml product strengths (applying a bracketing design), stored at 25°C/40% RH (36 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. At both storage conditions an increase in pH is observed as well as a linear increase in water loss. An increase in assay was also observed. No changes or trends were seen in any of the

other tested parameters and all results remained well within limits. Based on these results, the approved shelf life is 36 months. Results of the photostability studies do not indicate any degradation, photostability of the product is shown. Specific migration studies are performed showing no leaching substances in the product. No storage conditions are required.

After dilution in sodium chloride solution 0.9%, chemical and physical in use-stability has been demonstrated for 7 days at 20-22°C. Chemical and physical in-use stability with clonidine, morphine or fentanyl has been demonstrated for 40 hours at 20-22°C. The described concentrations, durations and storage conditions are described in the SmPC of the reference products and were also adopted in the SmPC of Levobupivacaine Molteni. Studies to demonstrate compatibility with diluents are not needed. As the proposed drug product is pharmaceutically equivalent with the reference product, containing the same components in comparable concentrations, it is very likely that the compatibilities and incompatibilities of the product are the same as for the reference product.

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 Levobupivacaine Molteni 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 Levobupivacaine Molteni 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 Chirocaine 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

Levobupivacaine 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

Levobupivacaine Molteni 0.625 mg/ml and 1.25 mg/ml solution for infusion, and Levobupivacaine Molteni 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml solution for injection/infusion are parenteral formulations and therefore fulfil 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 Levobupivacaine Molteni 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 products 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 Levobupivacaine Molteni.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Allergic reactions (anaphylactic shock), hypersensitivity • Severe bradycardia, hypotension and respiratory compromise with respiratory arrest • Cardiac disorders • CNS disorders • Neurological damage • Overdose
Important potential risks	• Inadvertent administration • Cauda Equina Syndrome (CES) • Off label use (intravenous regional anaesthesia (Bier's block), use in paracervical block in obstetrics)
Missing information	• 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 Chirocaine solution for injection/infusion. No new clinical studies were conducted. The MAH demonstrated equivalence based on comparative *in vitro* data. Risk management is adequately addressed. This generic 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 user test was performed on the PL for levobupivacaine 2.5 mg/ml and 5 mg/ml. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The age and gender distribution are considered acceptable. Sufficient questions were asked (12 specifically addressing the key safety message and an open question to provide feedback regarding lay-out). All participants were able to trace the information for the questions 100% of the time. Each of these participants showed they understood the information by answering the questions correctly >90% of the time. The PL is considered acceptable. User testing was carried out successfully.

The MAH has provided a bridging report for the levobupivacaine 0.625 mg/ml and 1.25 mg/ml, and 7.5 mg/ml package leaflets (daughter leaflets). The leaflets have been compared to the levobupivacaine 2.5 mg/ml and 5 mg/ml package leaflet (parent leaflet), for which a successful user test was conducted. The overall layout, design and writing style of both leaflets is the same, including the same booklet layout and the same headings, paragraph, and sentence structure. The daughter leaflets have

a slightly larger font size, which is considered acceptable. The key safety messages of both leaflets are the same. Bridging is therefore accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levobupivacaine Molteni 0.625 mg/ml and 1.25 mg/ml solution for infusion, and Levobupivacaine Molteni 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml solution for injection/infusion have a proven chemical-pharmaceutical quality and are generic forms of Chirocaine 0.625 mg/ml and 1.25 mg/ml solution for infusion, and Chirocaine 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml solution for injection/infusion. Chirocaine 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 Levobupivacaine Molteni with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 May 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
Change the QPPV and to update the summary of pharmacovigilance system	NL/H/3256/001-005/IA/001	IA	30-9-2015	30-10-2015	Approval	No