

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection  
L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A., Italy**

**ropivacaine hydrochloride**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1272/005/DC  
Registration number in the Netherlands: RVG 111003**

**11 April 2013**

Pharmacotherapeutic group:	anesthetics, local, amides
ATC code:	N01BB09
Route of administration:	intrathecal
Therapeutic indication:	surgical anaesthesia in adults
Prescription status:	prescription only
Date of authorisation in NL:	12 December 2012
Concerned Member States:	Decentralised procedure with DE, EL, IT, PL
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection from L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A. The date of authorisation was on 12 December 2012 in the Netherlands.

The product is indicated for intrathecal administration for surgical anaesthesia in adults. A comprehensive description of the indications and posology is given in the SPC.

Ropivacaine is a long-acting amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses Ropivacaine produces surgical anaesthesia, while at lower doses it produces sensory block with limited and non-progressive motor block.

The mechanism is a reversible reduction of the membrane permeability of the nerve fibre to sodium ions. Consequently the depolarisation velocity is decreased and the excitable threshold increased, resulting in a local blockade of nerve impulses.

The most characteristic property of ropivacaine is the long duration of action. Onset and duration of the local anaesthetic efficacy are dependant upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. adrenaline).

This decentralised procedure concerns change to the existing marketing authorisation leading to the addition of a new strength (line-extension): Ropivacaine Hydrochloride Molteni 5 mg/ml solution for injection. Ropivacaine Hydrochloride Molteni 2/7.5/10 mg/ml formulations (NL License RVG 101140, 101153, 101154, 101156) are already registered as generic medicinal products through decentralised procedure NL/H/1272/001-004. The innovator product is Naropin 2 mg/ml (NL RVG 18437), which has been registered in the Netherlands by Astra Zeneca since 1995. Naropin 5 mg/ml for intrathecal administration (NL RVG 27204) has been authorised since 4 March 2003. The marketing authorisation was subsequently recognised in other member states through MRP NL/H/0104/004.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Ropivacaine Hydrochloride Molteni 5 mg/ml, aqueous injection is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

The active substance is ropivacaine, an established active substance described in the European Pharmacopoeia 6.0 (Ph.Eur.\*). The active substance is very slightly soluble in water. Ropivacaine has one chiral centre and exhibits polymorphism.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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

Ropivacaine is manufactured in a two step process by one manufacturer, and in a three step process by the second supplier. The drug substance has been adequately characterized.

#### Quality control of drug substance

The drug substance specification is in line with the Ph.Eur., with additional requirements for residual solvents, loss on drying and water content. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

#### Stability of drug substance

Stability data on the active substance from the first supplier have been provided for three production-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). A small change in optical rotation and variability in absorbance is seen at both storage conditions. The drug substance is not sensitive to light. The claimed shelf life of the applicant of 24 months is justified. No special storage condition is required.

Stability data on the active substance from the second manufacturer have been provided for six production-scale batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months). No clear trends could be observed. The drug substance is not sensitive to light. The claimed retest period of 48 months is justified. No special storage condition is required.

\* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

#### **Medicinal Product**

##### Composition

Ropivacaine Hydrochloride Molteni 5 mg/ml is a sterile, clear, colourless, isotonic, isobaric aqueous solution with pH between 4.0-6.0 and osmolality of 267 – 310 mOsm/kg.

The solution for injection is packed in 10 ml transparent polypropylene ampoules in sterile plastic cover.

The excipients are: sodium chloride, hydrochloric acid 3.6% w/v (E507), sodium hydroxide (E524) (for pH-adjustment) and water for injection.

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The test product was compared to the innovator product with respect to appearance of solution, pH, assay, identification, related substances, enantiomeric purity, particulate contamination, osmolality and extractable volume. The products are similar.

The product is sterile and for single use only. The chosen container closure system prevents microbial contamination. No overages of the active ingredient or excipients have been used.

A bioequivalence study is not performed, since the drug product is an aqueous solution not to be administered intravenously, but consisting of the same active substance and excipients as the innovator product. 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. Sodium hydroxide is used to set the pH at 5.7. Before filling the ampoules the solution is filtered. The drug product is sterilised at 121°C for 15 minutes. The manufacturing process has been adequately validated according to relevant European guidelines for three production-scale batches of the already approved 2 and 10 mg/ml strengths. Process validation data on the proposed strength of drug product has not been presented, but is accepted based on bracketing.

#### 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.

#### Quality control of drug product

The product specification includes tests for appearance, identity, pH, assay, degradation, particulate matter, sterility, endotoxins, extractable volume, water loss, and osmolality. The release and shelf life requirements for the ampoules are identical, except for water loss, assay and osmolality. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three production-scale batches of the already approved 2 and 10 mg/ml strengths, demonstrating compliance with the release specification. Batch analysis data on the 5 mg/ml strength has been presented for one batch of the 10 mL fill and one batch of the 20 ml fill, demonstrating compliance with the specification.

#### Stability of drug product

Stability data on the product has been provided for 10 full-scale batches stored at 25°C/40% RH (36 or 12 months) and 30°C/35% RH (36 or 12 months) and 40°C/45% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline for semi-permeable containers. Three batches of the 2 and 10 mg/ml have been included in the studies. Bracketing is again applied for the proposed 5 mg/ml strength.

For all storage conditions an increase in water loss and assay is observed. Usage of an overfill of the of the bulk solution to compensate for the water loss is applied and is acceptable. A migration study reveals that no leeching substances are present after six months storage at accelerated storage conditions. A photostability study shows that the drug product is not sensitive to light.

The claimed shelf life of 36 months is justified for the ampoules. The storage condition “do not store above 25°C and do not refrigerate or freeze” is considered acceptable.

#### 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.2 Non-clinical aspects**

This product is a generic formulation of Naropin, which is available on the European market. 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.

### **Environmental risk assessment**

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ropivacaine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## **II.3 Clinical aspects**

Ropivacaine 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.

Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection is a parenteral formulation 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 of the same type of solution, contains the same active substance in the same concentration and has the same or comparable excipients as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The drug product is an aqueous solution not to be administered intravenously, but the quantitative composition of Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection 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 product can be used instead of its reference product.

### *Pharmacology*

Ropivacaine is a well-known long-acting local anaesthetic, which is commonly used in hospital settings for surgical anaesthesia and post-operative pain. The 5 mg/ml preservative-free isobaric formulation is developed for intrathecal use, also called spinal anaesthesia.

Spinal anaesthesia is induced by injecting small amounts of local anaesthetic into the cerebro-spinal fluid (CSF). The injection is usually made in the lumbar spine below the level at which the spinal cord ends (L2).

Potential benefits of this technique are that spinal anaesthesia is relatively easy to perform, and may provide favourable operating conditions for surgery below the umbilicus, such as hernia repairs, urological and gynaecological operations including sectio caesaria. Spinal anaesthesia provides intense muscle relaxation, which is required for lower abdominal and lower limb surgery. Blood loss during operation is less than when the same operation is done under general anaesthesia, because of a fall in blood pressure and heart rate and improved venous drainage at spinal anaesthesia. Spinal anaesthesia may be a safe alternative in those situations where general anaesthesia is complicated, such as in older patients and those with systemic disease, such as chronic respiratory disease, hepatic, renal and diabetes.

Drawbacks of spinal blocks are that patients stay awake and are aware of the operation. Hypotension may occur with higher blocks. Postural headache is common, and there is an enhanced risk of septic meningitis if no proper precautions are taken. A major limitation may be that a spinal block is not suitable for surgery lasting longer than approximately 2-6 hours. If an operation unexpectedly lasts longer than this, it may be necessary to convert to a general anaesthetic.

In the Clinical Overview, a summary of the literature is provided. In several randomised trials, ropivacaine provided similar duration of anaesthesia as bupivacaine, when administered in a 2:1 or 3:2 dose ratio. The off-set of motor blocks was however significantly shorter for ropivacaine than bupivacaine in several

studies. E.g. motor block was recovered at 200 minutes versus 270 minutes, in the study by Boztug et al.<sup>1</sup> (2006), in 90 subject undergoing arthroscopy of the knee ( $p=0.015$ ), and at 2.1 versus 3.9 h, in a study by McNamee et al. (2002)<sup>2</sup>, in 66 subject undergoing hip arthroplasty ( $p<0.001$ ). In a prospective, randomised, blind study, 50 mg lidocaine 10 mg/ml and 10 mg ropivacaine 5 mg/ml was compared in thirty patients undergoing outpatient knee arthroscopy (Fanelli et al., 2009)<sup>3</sup>. The efficacy of a spinal block induced with lidocaine or ropivacaine was equivalent. However, lidocaine was associated with a clinically relevant incidence of transient neurologic symptoms (TNS). Six lidocaine patients reported TNS (40%) as compared with no patient receiving ropivacaine ( $P=0.005$ ).

#### *Treatment in Paediatrics*

Ropivacaine is not indicated in children below the age of 12 years. This is agreed, as there is limited experience in the intrathecal use of ropivacaine in paediatrics, in contrast hyperbaric bupivacaine, which may serve as an alternative treatment for children of all age groups (Paediatric Workshare procedure DE/W/042/pdWS/001).

#### Risk management plan

The absence of an RMP is accepted. For the adult and adolescent indication, no RMP is necessary at the moment. Ropivacaine was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ropivacaine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product. It should be noted that an RMP is in place concerning the use of ropivacaine 2 mg/mL for single caudal epidural block to neonates and infants aged 0 to 12 months and for continuous epidural infusion to children, infants, and neonates aged 0 months to 12 years

#### **Product information**

##### SPC

The SPC has been updated according the current QRD template and the proposed wording of the RMS and CMSs.

##### Readability test

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 readability test was carried out on the leaflet of the approved strengths: Ropivacaine Hydrochloride Molteni 2 mg/ml, 7.5 mg/ml, 10 mg/ml solution for injection/infusion. The leaflet has been subsequently modified according to the use of Ropivacaine Hydrochloride 5 mg/ml. The modification introduced does not really impact on design, layout of the information and writing style and do not substantially change readability of the leaflet.

After a pilot test, a test consisting of two rounds was carried out with two times 10 participants. Application of the pilot test led to a number of layout and wording changes to the original leaflet, to aid users in finding and understanding the information. The results of user testing demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to express the information in their own words.

There were no changes suggested for the tested leaflet. Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the

<sup>1</sup> Boztug N, Bigat Z, Karsli B, Saykal N, Ertok E. Comparison of ropivacaine and bupivacaine for intrathecal anesthesia during outpatient arthroscopic surgery. J Clin Anesth 2006; 18: 521-525.

<sup>2</sup> McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L, Gustafsson U. Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml<sup>-1</sup> with bupivacaine 5 mg ml<sup>-1</sup> for major orthopaedic surgery. Br J Anaesth 2002; 89 (5): 702-706.

<sup>3</sup> Fanelli G, Danelli G, Zasa M, Baciarello M, Di Cianni S, Leone S. Intrathecal ropivacaine 5 mg/ml for outpatient knee arthroscopy: a comparison with lidocaine 10 mg/ml. Acta Anaesthesiol Scand 2009; 53: 109-115.

critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Naropin 5 mg/ml. Naropin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ropivacaine containing products.

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 Ropivacaine Hydrochloride Molteni 5 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 November 2012. Ropivacaine Hydrochloride Molteni 5 mg/ml, solution for injection was authorised in the Netherlands on 12 December 2012.

The date for the first renewal will be: 5 November 2017.

There were no post-approval commitments made during the procedure.



## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

**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