CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ropivacaine Hydrochloride Molteni 2 mg/ml, solution for infusion
Ropivacaine Hydrochloride Molteni 2 mg/ml, solution for injection
Ropivacaine Hydrochloride Molteni 7.5 mg/ml, solution for injection
Ropivacaine Hydrochloride Molteni 10 mg/ml, solution for injection

L. Molteni & C. dei F.LLi Alitti Società di Esercizio S.p.A., Italy

ropivacaine

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/1272/01-04/DC
Registration number in the Netherlands: RVG 101140, 101153, 101154, 101156

5 August 2009

Pharmacotherapeutic group:	anesthetics, local, amides
ATC code:	N01BB09
Route of administration:	epidural, perineural
Therapeutic indication:	surgical anaesthesia, acute pain management. 2 mg/ml only: acute pain management in paediatrics
Prescription status:	prescription only
Date of authorisation in NL:	27 November 2008
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 2 mg/ml, solution for infusion and Ropivacaine Hydrochloride Molteni 2 / 7.5 / 10 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 27 November 2008 in the Netherlands.

The product is indicated for:

Surgical anaesthesia
- Epidural blocks for surgery, including Caesarean section
- Major nerve blocks
- Field blocks

Acute pain management
- Continuous epidural infusion or intermittent bolus administration during postoperative or labour pain
- Field blocks
- Continuous peripheral nerve block via a continuous infusion or intermittent bolus injections, e.g. postoperative pain management.

Ropivacaine Hydrochloride Molteni 2 mg/ml solution for infusion (injection):
Acute pain management in paediatrics (per- and postoperative)
- Caudal epidural block in neonates, infants and children up to and including 12 years
- Continuos epidural infusion in neonates, infants and children up to and including 12 years

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 a generic application claiming essential similarity with the innovator products Naropin 2, 7.5 and 10 mg/ml solution for injection (NL RVG 18437, 18440, 18441 respectively) which have been registered in the Netherlands by Astra Zeneca since 1995. In addition, reference is made to Naropin authorisations in the individual member states (reference product).

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 2 mg/ml, aqueous solution for infusion and Ropivacaine Hydrochloride Molteni 2 / 7.5 / 10 mg/ml, aqueous solution for injection are products for parenteral use, these are 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.

No paediatric development programme has been submitted.

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 these product types 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. It is formulated as the S-enantiomer, as the R-enantiomer is associated with cardiac toxicity.

Manufacture
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/EMEA 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.

Ropivacaine is manufactured in a two step process. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents. Detailed information on the manufacture is included in the EDMF. The drug substance has been adequately characterized. The R-isomer is allowed at a maximum level of 0.5%. No racemisation occurs during the manufacturing process.

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

Stability
Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in polyethylene bags inside a fibre drum.
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 MAH of 24 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

Solution for injection
Ropivacaine Hydrochloride Molteni 2, 7.5 and 10 mg/ml contain as active substance 2, 7.5 and 10 mg of ropivacaine hydrochloride.

The solution for injection is packed in a 10 or 20 ml transparent polypropylene ampoules in sterile plastic cover, available in a pack of 5.

Solution for infusion
Ropivacaine Hydrochloride Molteni 2 mg/ml contains as active substance 2 mg of ropivacaine hydrochloride, and is a sterile, clear, colourless, isotonic, aqueous solution with pH between 4.0-6.0.

The solution for infusion is packed in a 100 ml or 250 ml transparent polypropylene bag in sterile plastic cover, available in a pack of 5.

All formulations are a sterile, clear, colourless, isotonic, aqueous solution with pH between 4.0-6.0.

The ampoules are overfilled with 3% of the bulk solution and the infusion bags are overfilled with 2 % bulk solution in order to ensure the extraction of the declared volume.

The excipients are: sodium chloride, hydrochloric acid 3.6% w/v (E507), sodium hydroxide (E524) (for pH-adjustment), 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, osmolarity and extractable volume. The products are not significantly different.
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 or infusion bags the solution is filtered. The packagings are sterilised.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three production scaled batches.
The MAH committed not to use batches of ropivacaine base close to the expiration date. These will be subjected to all the tests defined in the active substance release specifications before being used for product manufacturing.

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. For the infusion bags the release and shelf life requirements for the upper limits for assay and osmolality are not identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production scaled batches of the extreme strengths, demonstrating compliance with the release specification.

Stability tests on the finished product

Stability data on the product has been provided for 18 full scaled batches stored at 25°C/60% RH (18 or 24 months) and 30°/65% RH (18 or 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Three batches of each of the extreme strengths for each packaging and pack size have been included in the studies. For all storage conditions an increase in water loss is observed. At intermediate and accelerated storage conditions an increase in assay is observed for both packagings. Furthermore, for the infusion bags an increase in water loss of 7% is observed after 24 months storage at intermediate conditions. This is a significant change. Therefore, the storage condition "Store below 25ºC" is justified.
For the 100 ml infusion bags a 6% increase in assay is observed after 24 months for two batches. This is a significant change. Therefore, a shelf-life of 18 months has been granted for the bags.
The claimed shelf life of 24 months is justified for the ampoules. A study on fragmentation of the rubber in the injection port of the infusion bag is included and complies with the Ph.Eur.. The storage condition "do not refrigerate or freeze" is justified. The MAH has included an in use stability study at 25°C and 2-8°C for 24 hours. The results comply with the shelf life specification.
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.
Usage of an overage to compensate for the water loss has been proposed and is acceptable. However, the batches currently placed in the stability studies do not have this overage and do not comply with the parameter extractable volume at the end of shelf-life. The MAH therefore committed not to market these batches. Besides, the MAH committed to provide the results of the ongoing stability studies.

Based on the data provided, the following shelf life was granted:
For Ropivacaine Hydrochloride Molteni 2 mg/ml, 7,5 mg/ml and 10 mg/ml, solution for injection:
18 months; "store below 25ºC" and "do not refrigerate or freeze".
For Ropivacaine Hydrochloride Molteni 2mg/ml, solution for infusion:
2 years; "store below 25ºC" and "do not refrigerate or freeze".

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. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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.

Ropivacaine Hydrochloride Molteni 2/7.5/10 mg/ml, solution for injection and Ropivacaine Hydrochloride Molteni 2 mg/ml, solution for 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 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 2/7.5/10 mg/ml, solution for injection and Ropivacaine Hydrochloride Molteni 2 mg/ml, solution for infusion 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.

Treatment in adults
The drug is indicated for local or regional anaesthesia in surgery and acute pain management (peripheral nerve blocks, epidural anaesthesia, field blocks, ocular anaesthesia) including Caesarian section. Obstetric paracervical anaesthesia is however contraindicated, due to lack of clinical data and possible risk of maternal haemorrhage and fetal bradycardia (as was observed with other local anaesthetics).

Treatment in Paediatrics
Ropivacaine is indicated for acute pain management in paediatrics (per-and postoperative), specifically for caudal epifural block and continuous epidural infusion in neonates, infants and children up to 12 years. The use of ropivacaine in premature children has not been documented.

Risk management plan
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 postauthorisation 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.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product. If one or more member states wish to have separate SPCs for each strength, this will be dealt with nationally.

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 participants were of various age (range 20-76 years), sex (11 female, 9 male) and had a varying educational status. The test consisted of a pilot test followed by two rounds with 10 participants each. Twelve questions were asked about all parts of the leaflet. Also, general comments (lay-out, readability. etc) were asked. Key (safety) issues were defined. After the pilot round several amendments were made to the PIL in order to improve readability. After the first test round no amendments were considered necessary. The report is clear and of good quality. The results show that the package leaflet meets the criteria for readability as set in the *Guideline on the readability of the label and the package leaflet of medicinal products for human use*.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ropivacaine Hydrochloride Molteni 2 mg/ml, solution for infusion and Ropivacaine Hydrochloride Molteni 2 / 7.5 / 10 mg/ml, solution for injection have a proven chemical-pharmaceutical quality and are generic forms of Naropin. Naropin 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 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 2 mg/ml, solution for infusion and Ropivacaine Hydrochloride Molteni 2 / 7.5 / 10 mg/ml, solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 15 October 2008. The products were authorised in the Netherlands on 27 November 2008.

A European harmonised birth date has been allocated (15 September 1995) and subsequently the first data lock point for ropivacaine is September 2009. The first PSUR will cover the period from October 2008 to September 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 May 2013

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to provide the results of the ongoing stability studies.
- The MAH committed not to market the batches currently used in the stability studies.
- The MAH committed not to use batches of ropivacaine base close to the expiration date. These will be subjected to all the tests defined in the active substance release specifications before being used for product manufacturing.

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_{max}	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
$t_{½}$	Half-life
t_{max}	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
Change in the name of the medicinal product in Germany and Poland	NL/H/1272/ 001-004/IB/001	IB	20-1-2009	20-2-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; including batch control/testing	NL/H/1272/ 001-004/IA/002	IA	20-1-2009	3-2-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms	NL/H/1272/ 001-004/IA/003	IA	20-1-2009	3-2-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms	NL/H/1272/ 001-004/IA/003	IA	20-1-2009	3-2-2009	Approval	N