CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ropivacaïne HCl Fresenius Kabi 2 mg/ml, solution for infusion Ropivacaïne HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection Fresenius Kabi Nederland B.V., the Netherlands

ropivacaine (as 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/1575/001-005/DC
Registration number in the Netherlands: RVG 104941-104945

12 August 2010

Pharmacotherapeutic group:	anesthetics, local, amides
ATC code:	N01BB09
Route of administration:	epidural, perineural
Therapeutic indication:	surgical anaesthesia, acute pain management, acute pain management in paediatrics
Prescription status:	prescription only
Date of authorisation in NL:	27 May 2010
Concerned Member States:	Decentralised procedure with BE, CY, DK, EL, FI, FR, IT, NO, SE; all strengths except 5 mg/ml – DE, ES, LU, PT, UK; all except 2 mg/ml for infusion – BG, RO; all except 2 and 5 mg/ml for injection – SI; only 2 and 7.5 mg/ml for injection - IE
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 Ropivacaïne HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaïne HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection, from Fresenius Kabi Nederland B.V. The date of authorisation was on 27 May 2010 in the Netherlands.

The product is indicated for:

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

2. 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.

3. Acute pain management in paediatrics:
(per- and postoperative)
- Caudal epidural block in neonates, infants and children up to and including 12 years.
- Continuous epidural infusion in neonates, infants and children up to and including 12 years.

Ropivacaine HCl 5 mg/ml is indicated for intrathecal administration for surgical anaesthesia.

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 HCl 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 dependent upon the administration site and dose, but are not influenced by the presence of a vasoconstrictor (e.g. adrenaline (epinephrine)).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Naropin 2/5/7.5/10 mg/ml (NL License RVG 18437, 18439, 18440 and 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). As the innovator product has never been granted a marketing authorisation in several member states, reference is made to Naropin as registered in the Netherlands, which serves as a European 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 Ropivacaïne HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaïne HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection are products for parenteral use in aqueous solution, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their references products.

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 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 (Ph.Eur.*) as ropivacaine hydrochloride monohydrate. The active substance is a white, odorless crystalline powder, which is freely soluble in water, soluble in methanol, sparingly soluble in isopropanol and acetone. Ropivacaine has one chiral centre and exhibits polymorphism. It is formulated as the S-enantiomer, as the R-enantiomer is associated with cardiac toxicity.

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 drug substance is manufactured in a 7-step synthesis. No class 1 solvents or heavy metal catalysts are been used. All starting materials are sufficiently controlled.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph of ropivacaine HCl monohydrate, with additional requirements for residual solvents and microbiological purity and the limit for water content is tightened to represent the anhydrous form of the active substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three lab-scale and three pilot-scale batches stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). Under accelerated conditions some trends were seen, but all results remained within specifications. The proposed retest period of 24 months could be granted for the drug substance when stored in the original container to protect from moisture and light.

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

Medicinal Product

Composition
All formulations are sterile, clear, colourless isotonic ready-to-use solutions with a pH of 4.0 to 6.0 and an osmolality between 270 and 330 mOsmol/kg.

The drug product is packed in 100 ml or 200 ml polyolefin bags (freeflex®) or into 10 ml or 20 ml polypropylene ampoules in the following concentrations:
- 2 mg/ml in 10 ml, 20 ml, 100 ml and 200 ml
- 5 mg/ml in 10 ml
- 7.5 mg/ml in 10 ml and 20 ml
- 10 mg/ml in 10 ml and 20 ml.

The excipients are: sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injections.

The different concentrations are considered dose proportional as the excipients present result in the same osmolarity and pH.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The proposed product was compared to the innovator product with respect to qualitative composition, appearance, colour of solution, absorbance, weight loss, osmolality, pH, assay and impurity profile. The products are not significantly different. Essential similarity has been demonstrated.
A bioequivalence study is not performed, since the drug product is an aqueous solution consisting of the same amounts of active substance and the same excipients as the innovator product. No overage is applied. The specification for extractable volume complies with Ph.Eur. The Ph.Eur. monograph specifies that the extractable volume is not less than the nominal volume. This is acceptable.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by mixing of ropivacaine HCl and sodium chloride in water for injections until visually dissolved, pH adjustment when necessary, after which the solution is filtered before filling. The filled containers are sterilised by steam sterilisation. The ampoules may be secondarily packed in polycarbonate-HDPE blisters that will then be steam sterilized again.
Process validations have been performed for the solution for infusion on two pilot-scale batches and two batches of production scale. For the solution for injection, two batches were included for the 2 mg/mL concentration (one pilot and one production scale) and two pilot-scale batches of the 10 mg/mL concentration. Additional validation data for the proposed form-fill-seal process at one manufacturing site has been submitted.

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

Quality control of drug product
The product specification includes tests for appearance and colour of solution, absorbance, identity, pH, assay, degradation, particulate matter, osmolality, sterility, endotoxins, extractable volume and weight loss. The release and shelf life requirements for the ampoules and freeflex bags are identical, except for assay and extractable volume. The limits on bacterial endotoxins differ for the different concentrations. Re-evaluation of shelf-life limit of total impurities and R-isomer will be performed.
The analytical methods have been adequately described and validated. Batch analytical data have been provided on two production-scale and three pilot-scale batches of the infusion solution (2 mg/mL) and on one production-scale (2 mg/mL) and seven pilot-scale (2 mg/mL and 10 mg/mL) batches of the injection solution, demonstrating compliance with the release specification.

Container Closure System
The container closure systems were chosen as they can be used in form-fill-seal machines. For the PP ampoules reference is made to Ph.Eur. monograph 3.1.6 on *Polypropylene for Containers and Closures for parenteral Preparations.*
For the freeflex bags a migration study has been performed on the 2 mg/mL in 100mL container as it has the worst volume to surface ratio. Some migration products were found after 6 months at 40°C/25% RH and/or 12 months at 30°C/35% RH, and have been toxicologically evaluated. For the ampoules, a migration study was performed on the 10mL ampoules containing 2mg/mL or 10mg/mL. Some migration products were found after 6 months at 40°C/25% RH and/or 6 months at 25°C/40% RH, and have been toxicologically evaluated. As compliance with the Ph.Eur. has been shown for all plastic materials, including the presence of additives, and the drug product is an aqueous solution without surfactants and the pH lies within the range of 3 to 10, this is deemed acceptable. The efficacy of the packaging material to protect against microbiological contamination has been demonstrated by a container closure integrity test performed on the freeflex bags and the ampoules separately.

Stability of drug product
Stability data on the infusion product (2mg/mL) has been provided for one production-scale and one pilot-scale batch of 200ml and two pilot-scale batches of 100 ml stored at 25°C/40% RH (24 months), 30°C/35% RH (12 months) and 40°C/25% RH (6 months). Stability data on the blistered injection product (2mg/mL and 10mg/mL) has been provided for one production-scale (10mg/mL) and seven pilot-scale batches equally divided over the 2mg/mL and 10mg/mL and 10mL and 20mL ampoules stored at 25°C/40% RH (18 months), 30°C/25% RH (18 months), 30°C/35% RH (12 months) and 40°C/25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline for semi-permeable containers. The long term conditions 30°C/35%RH and 30°C/25%RH can also be considered as intermediate storage condition.
For all storage conditions and products an increase in weight loss, pH and assay is observed. For the infusion products at accelerated storage conditions significant changes have been observed for assay. Based on the stability results the following shelf life, packaging material and storage conditions have been granted: 24 months, in freeflex infusion bags; ‘do not store above 30°C’, ‘do not refrigerate or freeze’, and 24 months in (un)blistered PP ampoules; ‘do not refrigerate or freeze’.

Compatibility/In-use stability
A compatibility study has been performed on ropivacaine solution (1-2 mg/mL) with different concentrations of fentanyl citrate, sufentanyl citrate, morphin sulfate and clonidin HCl. It has been demonstrated that Ropivacaine Solution for Infusion/Injection 2 mg/ml is compatible and physico-chemically stable with the tested medicinal products for a period of 24 h at 2-8°C and after 30 days at 20 – 30°C in line with the statement in the SPC of the innovator.

Several commitments have been made with regard to the finished product; these can be found on page 8 of this report.

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 HCl Fresenius Kabi 2 mg/ml, solution for infusion and l Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection 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 HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaine HCl Fresenius Kabi 2, 5, 7.5 and 10 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 products can be used instead of their reference products.

Efficacy/safety
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 Caesarean 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 epidural 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 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.
The following issues will be monitored and specifically reported upon in the PSURs:
- Local neurotoxicity/ neurological disorders for which the applicant should ensure long-term follow-up (facilitated by for instance a questionnaire)
- Cardiovascular events, hepatobiliary events and reports suggesting vasoconstriction
- Overdose, medication error cases and off-label use in premature neonates.

The SPC for the product will follow and be kept in line with that of the innovator.
The MAH will follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc.

Product information

SPC
The SPC is in accordance with that accepted for the reference product Naropin marketed by Astra Zeneca.

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 test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. The participants were questioned about the leaflet in an evaluation and problem-seeking test. The report details the demographic data of the volunteers, age, gender, social grade and education. For this user testing adults of both genders, aged 18-74 years, with varying educational level were included.
The questionnaire for this user test contained 14 questions specific to the key safety issues of Ropivacaine and 3 general questions on the format of the leaflet. The questions sufficiently address the key safety messages. After the pilot round, the lay-out was improved resulting from comments of the participants. After the first round of testing no further amendments were considered necessary.
The results show the PIL meets the criteria as set in the Readability Guidelines.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ropivacaïne HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaïne HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection have a proven chemical-pharmaceutical quality and 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 HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaine HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 March 2010. Ropivacaine HCl Fresenius Kabi 2 mg/ml, solution for infusion and Ropivacaine HCl Fresenius Kabi 2, 5, 7.5 and 10 mg/ml, solution for injection were authorised in the Netherlands on 27 May 2010.

A European harmonised birth date has been allocated (15 September 1995) and subsequently the first data lock point for ropivacaine is September 2012. The first PSUR will cover the period from March 2010 to September 2012, 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 present the requested comparative data for the 7.5 mg/ml when available.
- The MAH committed to present the requested certificates of analysis for the 5 mg/ml and 7.5 mg/ml concentrations of the first batches produced for the market.
- The MAH committed to re-evaluate the limit for total impurities at the end of the stability studies
- The MAH committed to place the first three full production-scale batches of the 2mg/mL solution for infusion in freeflex bags and three batches of the extremes on stability studies (2 mg/ml in 10 ml, 2 mg/ml in 20 ml, 10 mg/ml in 10 ml and 10 mg/ml in 20 ml, including the two full-scale ampoule batches already provided).

Pharmacovigilance/Risk management

- The MAH committed to monitor and specifically report upon several issues in the PSURs (see page 6). The SPC for the product will follow and be kept in line with that of the innovator and the MAH will follow, where appropriate, the risk minimisation activities of the innovator.

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