Public Assessment Report

Scientific discussion

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion

Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion

(levobupivacaine hydrochloride)

NL/H/2881/001-005/DC

Date: 28 October 2014

This module reflects the scientific discussion for the approval of Levobupivacaïne Fresenius Kabi. The procedure was finalised on 21 April 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 8-10.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion, and Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion, from Fresenius Kabi Nederland BV.

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion are indicated for:
Pain management
Continuous epidural infusion, for the management of post operative pain and labour analgesia.

Levobupivacaïne Fresenius Kabi 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, perineural (peripheral nerve block).
Minor, e.g. infiltration (including 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: perineural (ilioinguinal/iliohypogastric blocks).

Levobupivacaïne Fresenius Kabi 7.5 mg/ml solution for injection/infusion is indicated for:
Adults and adolescents (≥ 12 years)
Surgical anaesthesia
Major, e.g. epidural (except obstectric use), intrathecal, perineural (peripheral nerve block).
Minor, e.g. infiltration, (including 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. Chirocaine 0.625 mg/ml and 1.25 mg/ml, solution for infusion by Abbott Scandinavia AV has been registered in Sweden since November 2002. Chirocaine 2.5 mg/ml, 5 mg/ml, and 7.5 mg/ml solution for injection/concentrate for solution for infusion by Abbott Scandinavia AV has been registered in Sweden since December 1998.

The concerned member states (CMS) involved in this procedure were:
NL/H/2881/001/DC - ES, FR, IE, IT, NO, PL, UK
NL/H/2881/002/DC - BE, ES, FR, IE, IT, NO, PL, SI, UK
NL/H/2881/003/DC - BE, ES, FR, IE, IT, NO, PL, PT, RO, SI, UK
NL/H/2881/004/DC - BE, CZ, ES, FR, HR, IE, IT, NO, PL, PT, RO, SI, SK, UK
NL/H/2881/005/DC - BE, CZ, ES, FR, IE, IT, NO, PL, PT, RO, SI, SK, UK

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

II. QUALITY ASPECTS

II.1 Introduction

Levobupivacaïne Fresenius Kabi is a clear colourless aqueous solution with pH 4.0-6.0.

The drug product is packed in polyolefin bags (freeflex) for the 0.625 mg/mL and 1.25 mg/mL strengths with a fill volume of 100 ml or 200 ml, and in polyethylene ampoules (10 mL) for the other three strengths.

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

II.2 Drug Substance

The drug substance levobupivacaine hydrochloride is well-known but is not described in the European Pharmacopoeia (Ph.Eur.). However, a Ph.Eur. monograph is available for bupivacaine hydrochloride.

It is a white crystalline powder or colorless crystals, which is freely soluble in water and in alcohol, and slightly soluble in chloroform and acetone. Levobupivacine hydrochloride used in the finished product is crystalline anhydrous in nature. The molecule has one chiral center and it is the 'S' enantiomer.

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 by means of three synthetic steps and a refining step, followed by one synthetic step and a salt formation in order to obtain the final drug substance. The proposed starting materials are acceptable, and the synthetic process is described in sufficient detail.
This is sufficient to ensure full control of the quality of the final drug substance.

Quality control of drug substance
In general the specification is based on the Ph.Eur. monograph for bupivacaine hydrochloride with some specific adaptations for this single enantiomer and the catalysts and solvents used in the synthesis. Batch analysis data on three batches is provided.

Stability of drug substance
Stability data is provided on 3 batches stored at 30°C/65%RH (up to 12 months) and 40°C/75%RH (up to 6 months). Under both accelerated and long term conditions no up- or downward trends are observed for any of the parameters tested. Hence, the proposed re-test period of 12 months when stored below 25°C in a light resistant container can be granted.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The development studies performed were regarding characterisation of the innovator product, exposure to up to three autoclave cycles and heat sensitivity studies. The excipients used in the product are well known. The drug product packaged in the freeflex bags as well as in the polypropylene ampoules is terminally sterilised. The choice of sterilisation method is justified. Comparative studies were performed with the corresponding strengths of the reference product Chirocaine® in order to evaluate the comparability of the current drug products and the originator product with regard to physico-chemical characteristics, assay and the impurity profile. The data provided adequately show that the products for registration are comparable with the corresponding strengths of the reference product.
The choices of the packaging and manufacturing process are justified.

Manufacturing process

The manufacturing process for the polyolefin bags differs slightly from that for the polypropylene ampoule. Both are standard processes. The components are weighed and dissolved in water for injections. The pH is measured and if necessary adjusted with NaOH or HCl. The chloride content is controlled and the volume is adjusted to final volume with water for injections. The pre-cleaned lines, filter and filling machines are flushed with solution prior to filling.
The filling of polypropylene ampoule is performed using the blow-fill-seal technology, where during one continuous cycle containers are formed, filled and sealed. The polypropylene ampoules are sterilised. The polyolefin bags are filled automatically with a controlled volume to meet the specification for extractable volume. The filled bags are sealed. Each bag is supplied with a sealed overpouch before sterilisation.
Process validation data on the product have been presented for three commercial-scale batches for both presentations. This is sufficient.

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

Microbiological attributes
As the drug product is intended for parenteral use, it has to be sterile according to Ph.Eur. 2.6.1 and the sterility of the drug product has to be ensured by applying a suitable sterilisation procedure according to Ph.Eur. 5.1.1. The microbiological attributes are adequately controlled.

Quality control of drug product
The product specification includes tests for appearance, degree of colouration, pH, osmolality, extractable volume, water loss (shelf-life limit), identification (release limit), assay, related substances, visible and sub-visible particles, sterility and bacterial endotoxins. Except for assay and one related substance, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three batches per presentation. The results comply with the proposed specifications.

Stability of drug product
Stability data on four commercial-scale batches of the 0.625 mg/mL and four batches of the 1.25 mg/mL presentation of the drug product (both in a 200 mL and a 100 mL polyolefin bag) have been provided. These were stored at 25°C/40%RH, 30°C/35%RH and 40°C/NMT 25%RH up to 18 or 6 months.
For the products packaged in the polypropylene ampoules stability data on two batches of the 2.5 mg/mL and two batches of the 7.5 mg/mL strength have been provided. These were also stored at 25°C/40% RH, 30°C/35%RH and 40°C/NMT 25%RH up to 18 or 6 months.
The conditions used in the stability studies are in accordance with the Guideline on stability testing (CPMP/QWP/122/02, rev 1 corr) regarding finished products packaged in semi-permeable containers. All batches comply with the proposed set of specifications, at all temperatures tested. The only visible trend is the temperature dependent increase in weight loss, which is common for these types of packages, and a corresponding increase in the assay values was observed. The drug product was demonstrated to be photostable.
The proposed shelf-life of 24 months without specific storage conditions is justified for both package types.

The compatibility of the drug product was shown with the solutions containing the active substances listed in the SmPC of the innovator. The drug product was examined at concentrations of 0.625 mg/ml and 1.25 mg/ml. This is acceptable since according to the SmPC, in cases where levobupivacaine is combined with other agents *e.g.* opioids in pain management, the levobupivacaine dose should be reduced and use of a lower concentration (*e.g.* 1.25 mg/ml) is preferable. In-use stability was shown for 30 days.

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 Levobupivacaïne Fresenius Kabi 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 Levobupivacaïne Fresenius Kabi solution for injection/infustion 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 tot 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

Levobupivacaïne Fresenius Kabi is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Levobupivacaïne Fresenius Kabi is essentially the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levobupivacaïne Fresenius Kabi solution for injection/infusion.

- Summary table of safety concerns as approved in RMP

Important identified risks	Allergic reactions (anaphylactic shock) Hypersensitivity Severe bradycardia Hypotension and respiratory compromise

	with cardiac arrest Neurological damage
Important potential risks	Cauda Equina Syndrome (CES) Off label use (intraveneous regional anaesthesia (Bier's block), use in paracervical block in obstetrics)
Missing information	Use in first-trimester (early) pregnant women

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. Based on in-vitro and literature data, the MAH sufficiently justified that the pharmacokinetic profile of the product will be similar to the pharmacokinetic profile of this reference product. The RMP is acceptable. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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. A full readability report was provided for Levobupivacaïne Fresenius Kabi 7.5 mg/ml solution for injection/infusion. For the other strengths a bridging report is provided. This is acceptable.
The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion, and Levobupivacaïne Fresenius Kabi 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 Levobupivacaïne Fresenius Kabi with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 21 April 2014.

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

Summary Public Assessment Report

Generics

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion

Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion

(levobupivacaine)

NL/H/2881/001-005/DC

Date: 28 October 2014

Summary Public Assessment Report

Generics

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion
Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion

Active substance: levobupivacaine hydrochloride

This is a summary of the public assessment report (PAR) for Levobupivacaïne Fresenius Kabi. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Levobupivacaïne Fresenius Kabi solution for injection or infusion.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is this medicine and what is it used for?
Levobupivacaïne Fresenius Kabi is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Chirocaine solution for injection or infusion.

Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml solution for infusion is used for pain relief in adults only:
- after major surgery
- during childbirth

Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion is used:

In adults and adolescents (12 years of age and older):
Levobupivacaïne Fresenius Kabi is used as a local anaesthetic to numb parts of the body before major surgery and minor surgery (such as on the eye and mouth). The 2.5 mg/ml and 5 mg/ml strengths can be used as an epidural for caesarean section. The 7.5 mg/ml solution for injection/infusion must not be used for caesarean section.

It is also used for pain relief:
- after major surgery
- during childbirth (2.5 mg/ml and 5 mg/ml only)

In children (below the age of 12):
Levobupivacaïne Fresenius Kabi can also be used with children to numb parts of the body before surgery and for pain relief after minor surgery, such as the repair of a groin hernia.

How does this medicine work?
Levobupivacaine Kabi belongs to a group of medicines called local anaesthetics. This type of medicine is used to make an area of the body numb or free from pain.

How is this medicine used?
The pharmaceutical form of Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml is a solution for infusion and the route of administration is epidural. This means that the medicine is administered through a small tube placed in the epidural space by an insertion in patient's back.

The pharmaceutical form of Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml is a solution for injection/infusion. This medicine is administered through a needle or into a small tube in the epidural space. It can also be injected into other parts of the body to numb the area that will be treated, such as the eye, arm or leg.

These medicines can only be obtained with a prescription.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has this medicine been studied?
No additional studies were needed as Levobupivacaïne Fresenius Kabi is a generic medicine that is given by an infusion or injection and contains the same active substance as the reference medicine, Chirocaine.

What are the possible side effects of this medicine?
Because this is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of all side effects reported with Levobupivacaïne Fresenius Kabi, see section 4 of the package leaflet.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, this medicine has been shown to be comparable to Chirocaine. Therefore, the Medicines Evaluation Board of the Netherlands decided that, as for the reference medicine, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Levobupivacaïne Fresenius Kabi, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine
In the Netherlands, the marketing authorisation for Levobupivacaïne Fresenius Kabi 0.625 mg/ml and 1.25 mg/ml, solution for infusion and Levobupivacaïne Fresenius Kabi 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml, solution for injection/infusion was granted on 26 June 2014.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human. For more information about treatment with Levobupivacaïne Fresenius Kabi, read the package leaflet (0.625 mg/ml and 1.25 mg/ml: http://mri.medagencies.org/download/NL_H_2881_001_FinalPL.pdf; 2.5 mg/ml and 5 mg/ml: http://mri.medagencies.org/download/NL_H_2881_003_FinalPL.pdf; 7.5 mg/ml: http://mri.medagencies.org/download/NL_H_2881_005_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in October 2014.