CBG MEB

Public Assessment Report

Scientific discussion

Sufentanil Eurocept 5 microgram/ml and 50 microgram/ml, solution for injection

(sufentanil citrate)

NL License RVG: 114609, 114610

Date: 9 November 2018

This module reflects the scientific discussion for the approval of Sufentanil Eurocept 5 microgram/ml and 50 microgram/ml, solution for injection. The marketing authorisation was granted on 26 May 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Sufentanil Eurocept 5 microgram/ml and 50 microgram/ml, solution for injection from Eurocept International B.V.

The product is indicated for:

Use in adults
- Intravenous pain control for surgical interventions under general anaesthesia.
- Postoperative epidural pain control (including caesarean section).
- Epidural analgesia in combination with bupivacaine during labour and vaginal delivery.

Use in children
- Intravenous sufentanil is indicated as an analgesic agent for use during induction and/or maintenance of balanced general anaesthesia in children over the age of 1 month.
- Epidural sufentanil is indicated in children aged 1 year and over for the postoperative management of pain following general surgery, thoracic or orthopaedic procedures.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Sufenta 0.005 mg/ml solution for injection (NL Licence RVG 09233) which has been registered in The Netherlands by Janssen-Cilag B.V. since 22 June 1982.

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

II. QUALITY ASPECTS

II.1 Introduction

Sufentanil Eurocept is a clear and uncoloured solution for injection. The product is available in two strengths.

The 5 µg/ml strength is packed in a 2 ml or 10 ml type I transparent glass ampoule. The 2 ml ampoule is coded with two coloured rings around the ampoule neck (red upper ring and green lower ring) and a red dot. The 10 ml ampoule is coded with one yellow ring and a yellow dot.
The 50 µg/ml strength is packed in a 1 ml or a 5 ml type I transparent glass ampoule. The 1 ml ampoule is coded with two pink coloured rings and a black dot. The 5 ml ampoule is coded with one black coloured ring and a black dot.

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

II.2 Drug Substance

The active substance is sufentanil citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Sufentanil Eurocept is a white to off-white powder. It is practically insoluble in water, freely soluble in ethanol (96%) and in methanol. The same crystalline form or the same mixture of crystalline forms of sufentanil base is manufactured.

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 synthetic route is provided as a flow chart which includes the chemical names and lists the solvents used in each of the eight steps. Sufficient information has been provided. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification meets the requirements of the monograph in the Ph.Eur. and includes additional requirements for specified impurities. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six batches stored at 25°C/60% RH for up to 36 months. No significant changes are seen. Based on the data submitted a retest period could be granted of 36 months when stored below 25°C can be granted.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. In order to avoid possible oxidation of the drug substance nitrogen is used during the production and as a head space gas. The drug product can be sterilised by means of autoclaving.

Manufacturing process
The manufacturing process is a straight forward process of dissolving the ingredients in water for injection, pH adjustment, filtration, filling and closing of the ampoules, and terminal sterilisation.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for five commercial scale (including full scale) batches of the 5 µg/ml strength and for three full scale batches of the 50 µg/ml strength in accordance with the relevant European guidelines.

Control of excipients
The excipients used in the drug product comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification and includes tests for appearance, identity, pH, extractable volume, osmolality, assay, degradation products, particulate matter, sterility, and endotoxins. With the exception of a separate end of shelf-life limit for the pH, the release and end of shelf-life limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from five production scale batches of the 5 µg/ml strength and three production scale batches of the 50 µg/ml strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for five batches of the 5 µg/ml strength and three batches of the 50 µg/ml strength. The batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months).
In all batches and at both storage temperatures only an increase in the pH value was seen. All other parameters tested remained stable. Results of a photostability study have not been included.

On the basis of the current stability data the claimed shelf-life of three years when stored in the outer package in order to protect from light can be granted.

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 MEB considers that Sufentanil Eurocept 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 Sufentanil Eurocept 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 Sufenta which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sufentanil citrate 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Sufentanil Eurocept 5 microgram/ml and 50 microgram/ml, solution for injection 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 Sufentanil Eurocept 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.

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 Sufentanil Eurocept.

Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Bradycardia and cardiac arrest • Hypotension • MAO inhibitors • Use in lactation
Important potential risks	• Use in pregnancy
Missing information	• Serotonin syndrome

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sufenta. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

This product should only be administered by health care professionals specialising in anaesthesia-resuscitation or in emergency medicine and who are familiar with the use of anaesthetics, or under their supervision, and who have all the necessary anaesthesia-resuscitation equipment.
Therefore, the consultation with target patient groups is not applicable for this product.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sufentanil Eurocept 5 microgram/ml and 50 microgram/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Sufenta 0.005 mg/ml solution for injection. Sufenta 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.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Sufentanil Eurocept was authorised in the Netherlands on 26 May 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Grouped variation	IA	29-6-2017	8-8-2017	Approval	N
Update of the ASMF	II	22-8-2017	21-2-2018	Approval	Y