CBG MEB

Public Assessment Report

Scientific discussion

Alfentanil-hameln 0.5 mg/ml solution for injection

(alfentanil)

NL/H/3451/001/DC

Date: 7 March 2017

This module reflects the scientific discussion for the approval of Alfentanil-hameln 0.5 mg/ml solution for injection. The procedure was finalised on 25 March 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Alfentanil-hameln 0.5 mg/ml solution for injection, from hameln pharmaceuticals ltd.

Alfentanil-hameln is indicated in adults:
- as an analgesic supplement for the induction of anaesthesia
- as an adjunct in the maintenance of general anaesthesia

Due to its rapid and short lasting action, alfentanil is used as an opioid analgesic for short procedures and outpatient surgery as well as an analgesic supplement for procedures of medium and long duration, since periods with increased pain can be managed by small alfentanil supplements or adapting the rate of infusion.

Alfentanil-hameln is indicated for use in neonates, infants, and children:
- as an opioid in association with a hypnotic to induce anaesthesia
- as a narcotic analgesic in association with general anaesthesia and for both short and long surgical procedures

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 Rapifen 0.5 mg/ml solution for injection which has been registered in Austria by Janssen-Cilag Pharma GmbH since 30 March 1987. In the Netherlands, the innovator product Rapifen 0.5 mg/ml, solution for injection (NL License RVG 09860) has been registered by Janssen-Cilag B.V. since 9 March 1983.

The concerned member states (CMS) involved in this procedure were Austria, Finland, Norway, Portugal and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Alfentanil-hameln is a clear and colourless solution for injection with pH 4.0 - 6.0 and osmolality 270 - 310 mOsmol/kg.

Each ml solution contains 500 micrograms alfentanil, as 543.8 micrograms alfentanil hydrochloride.

The solution is packed in 2 ml and 10 ml colourless glass ampoules (type I) or in 50 ml colourless glass vials (type I) with bromobutyl rubber stopper and aluminium cap.

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

II.2 Drug Substance

The active substance is alfentanil hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water, ethanol and methanol. It is a white or almost white powder. Polymorphism is not considered relevant in view of the dosage form.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the

chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Assessment of the manufacturing process was performed by the EDQM upon granting the CEPs. It has been stated on the CEPs that water is used in the final step of the synthesis. As the substance is used for a parenteral product, the quality of the water was confirmed. Reference has been made to the Note for Guidance (NfG) *on Quality of water for pharmaceutical use*.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEPs, with additional requirements for specific impurities, residual solvents, a residual catalyst and sulphated ash. In addition, a non-routine test has been added for microbiological purity.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches of each manufacturer. Based on the results, non-routine testing of microbiological purity is acceptable.

Stability of drug substance
The active substance has a re-test period of 5 years (manufacturer-I) and 2 years (manufacturer-II). Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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. The pH limit of the product has been justified. The manufacturing process has been adequately developed and includes bioburden reduction by filtration followed by sterilisation in the final container. The container closure system is common for this dosage form.

No bioequivalence study is required since the drug product concerns a parenteral solution, which has the same drug substance concentration as the innovator product. The compatibility of the drug product with glucose 5% solution, sodium chloride 0.9% solution, glucose 5% + sodium chloride 0.9% solution and Ringer's lactate after dilution to 25 µg/ml or 80 µg/ml has been demonstrated. The chosen dilution range is acceptable in view of the dosing schedule.
The pharmaceutical development of the drug product was considered to be adequately performed.

Manufacturing process
The manufacturing process consists of compounding, filtration, filling and terminal sterilisation. Two manufacturing sites are stated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for sufficient full scaled batches from manufacturer-I and pilot scaled batches from manufacturer-II. The MAH committed to perform process validation for full scaled batches from manufacturer-II post authorisation.

Control of excipients
The excipients 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 includes tests for appearance, identity, assay, degradation, particulate matter, sterility, endotoxins, extractable volume and pH. The release and shelf-life requirements are identical and are acceptable. 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 12 full scaled batches (manufacturer-I) and 4 pilot scaled batches (manufacturer-II) have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on several pilot and commercial scaled batches stored at 25°C/60% RH (up to 36 months), 30°/75% RH (up to 24 months) and 40°C/75% RH (6 months) as well as one full scaled commercial batch (up to 12 months at 30°C/75% RH). The conditions used in the stability studies are not fully according to the ICH stability guideline, but there is no objection to the higher humidity at 30°C (75% in stead of 65%). The batches were stored in glass vials or glass ampoules. In addition a photostability study was performed. No changes are seen, hence the proposed shelf-life of 3 years with no specific storage restriction is justified.

In-use stability studies demonstrate that the product remains stable for 48 hours following dilution, when stored at room temperature. From a microbiological point of view, the product should be used immediately.

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 Alfentanil-hameln has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH has committed to perform validation testing (including holding time verification) on the manufacturing process at commercial scale at manufacturer-II.
- The MAH has committed to store one more batch at accelerated conditions and one more batch at long-term and accelerated conditions, and to continue the ongoing stability studies up to the proposed shelf-life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Alfentanil-hameln 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 Rapifen 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Alfentanil hydrochloride 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

Alfentanil-hameln 0.5 mg/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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Alfentanil-hameln 0.5 mg/ml 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 Alfentanil-hameln.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Respiratory depression (including concomitant use with strong CYP3A4 inhibitors and with other centrally depressing agents) • Bradycardia and cardiac arrest • Hypotension • Interaction with MAO inhibitors resulting in serotonin syndrome
Important potential risks	• Use in pregnancy and lactation • Medication error
Missing information	None

The member states 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 Rapifen. No new clinical studies were conducted. Alfentanil-hameln is a parenteral formulation and fulfils the requirements for an exemption from bioequivalence studies. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Alfentanil 5 mg/ml solution for injection (Hameln pharmaceuticals ltd). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Alfentanil-hameln 0.5 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Rapifen 0.5 mg/ml solution for injection. Rapifen 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 Alfentanil-hameln with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 March 2016.

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
Secondary packaging site	NL/H/3451/ 001/IA	IA	21-11-2016	14-12-2016	Approval	No