COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fentanyl Kalceks 0.05 mg/ml, solution for injection

(fentanyl citrate)

NL/H/5121/001/MR

Date: 11 August 2020

This module reflects the scientific discussion for the approval of Fentanyl Kalceks 0.05 mg/ml, solution for injection. The procedure was finalised at 1 July 2020. 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 Member States have granted a marketing authorisation for Fentanyl Kalceks 0.05 mg/ml, solution for injection, from AS KALCEKS.

The product is an anaesthesia analgesic:
- for use as an opioid analgesic supplement in general or local anaesthesia;
- for administration with a neuroleptic.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Sublimaze 50 mcg/ml solution for injection which has been registered in the United Kingdom by Janssen-Cilag Limited on 26 February 1980. Piramal Critical Care Limited is currently the Marketing Authorisation Holder. In the Netherlands, innovator product has been registered since 12 July 1982 as Fentanyl-Piramal 0.05 mcg/ml solution for injection (NL License RVG 04748).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Denmark, Finland, Hungary, Ireland, Norway, Romania, Spain, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Fentanyl Kalceks is a clear, colourless solution for injection, free from visible particles. The pH of the solution is 4.0 to 7.0. Osmolality is approximately 285 mOsmol/kg. Each ml of solution contains 50 micrograms of fentanyl (as fentanyl citrate).

The solution is packed in glass ampoules (2 ml or 10 ml).

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

II.2 Drug Substance

The active substance is fentanyl citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fentanyl citrate is white or almost white powder and soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96%).

The CEP procedure is used by both manufacturers for 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

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches of manufacturer-I and two batches of manufacturer-II.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. 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. Information is presented about the product and manufacturing development. The choice of excipients is justified and their functions explained.

The formulation was changed to include sodium chloride at a concentration of 0.9%, to create an isotonic solution. The addition of sodium chloride at a concentration of 0.9% is not expected to affect the manufacturing process, interaction of the drug product with the primary packaging or the storage conditions and shelf-life of the drug product. No information is presented about process characterisation, e.g. identification of critical process steps related critical quality attributes and (critical) process parameters. However, since the manufacturing process is considered straightforward and overall appropriate controls are applied, further detailed information about the manufacturing process development is not

deemed necessary. Appropriate release acceptance criteria are set in compliance with Ph.Eur. Overall, pharmaceutical development has been adequately performed.

Manufacturing process

The product is manufactured using standard manufacturing techniques, and includes weighing of active ingredients and excipients, preparation of the solution, sterilising filtration, filling and sealing of ampoules, steam sterilisation, product control, labelling, and packaging. The manufacturing process is straightforward, the process description and flow chart include sufficient details on the experimental conditions and the process parameters routinely applied. The manufacturing process has been validated appropriately. Process validation data on the product has been presented for three full scale production batches for the 2 ml presentation, and one full scale batch and one small batch for the 10 ml presentation in accordance with relevant European guidelines.

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, pH, extractable volume, particulate contamination, related substances (impurities), fentanyl content (assay), sterility and bacterial endotoxins. 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 four full scale batches (3x 2 ml, 1x 10 ml presentation) and one small scale batch (1x 10 ml presentation) from the proposed production site have been provided, demonstrating compliance with the specification.

Microbial attributes

The manufacturing process includes a filtration step as well as a terminal sterilisation step. Moreover, endotoxin and sterility testing is routinely performed as part of the batch release procedure. Appropriate release acceptance criteria are set in compliance with Ph.Eur. Collectively, these measures sufficiently assure the microbiological quality of the product.

Stability of drug product

Stability data on the product has been provided for three full scale batches of both the 2 ml and 10 ml ampoule presentation. Forty-eight months stability data is available for the 2 ml and 10 mL presentation when stored at 25°C/60% RH and six months stability for samples stored at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the same packaging as that of the marketed product.

Stability data for long-term storage at 25°C/60% RH and accelerated storage at 40°C/75% RH for the 2 ml and 10 ml batches demonstrate that all parameters comply with the quality specification requirements after four years long-term storage and after 6 months accelerated storage. Based on the presented stability data, the proposed shelf life of 4 years,

without special temperature storage conditions, and protected from light (do not freeze) is justified.

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 Fentanyl Kalceks 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 Fentanyl Kalceks 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 Sublimaze 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

Fentanyl 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

Fentanyl Kalceks 0.05 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 Fentanyl Kalceks 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 Fentanyl Kalceks.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Cardiovascular depression • Abuse, misuse and dependence • Serotonin syndrome induced by interaction between fentanyl and serotonergic drugs
Important potential risks	None
Missing information	• Use in children under 2 years of age • Use in patients with renal or hepatic dysfunction • Use in pregnant or breast-feeding woman

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 Sublimaze. 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

The package leaflet (PL) 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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Fentanyl Kalceks 0.05 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Sublimaze 50 mcg/ml solution for injection. Sublimaze 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. A biowaiver has been granted.

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 Fentanyl Kalceks with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 1 July 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse