COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fentanyl CF 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1200 microgram and 1600 microgram, lozenges with integral applicator for oromucosal use

(fentanyl citrate)

NL/H/4053/001-006/DC

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This module reflects the scientific discussion for the approval of Fentanyl CF 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1200 microgram and 1600 microgram, lozenges with integral applicator for oromucosal use. The procedure was finalised at 10 January 2019. 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 CF 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1200 microgram and 1600 microgram, lozenges with integral applicator for oromucosal use, from Centrafarm B.V.

The product is indicated for management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of persistent pain controlled by other means.

Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Sublimaze 50 mcg/ml solution for injection which has been registered in the UK by Janssen-Cilag Limited since 26 February 1980. In the Netherlands, Fentanyl Janssen 0.05 mg/ml solution for injection has been registered since 12 July 1982 (NL Licence RVG 04748).

The clinical basis of the present submission rests on the demonstration of bioequivalence with the product Actiq 200 µg, 400 µg, 600 µ, 800 µg, 1200 µg and 1600 µg compressed lozenge with integral oromucosal applicator, authorised in Spain. Actiq was first introduced into the market in 2000 in the United Kingdom as an abridged dossier to Sublimaze.

The concerned member states (CMS) involved in this procedure were Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the innovator product consists in a different pharmaceutical form.

II. QUALITY ASPECTS

II.1 Introduction

Fentanyl CF is a white or slightly yellowish cylindrical lozenge, on which its respective dosage strength is printed, attached to a plastic handle at the opposite end also labelled with the dosage strength. The lozenges may develop brownish spots during storage. The lozenges contain 200, 400, 600, 800, 1200 or 1600 microgram fentanyl (as citrate).

The compressed lozenges are packed in a child-resistance and opaque PVC-PCTFE-PVdC-PVC/Al blisters.

The excipients are:
Compressed lozenge - dextrates hydrated, anhydrous citric acid, anhydrous disodium phosphate, magnesium stearate and artificial berry flavour (main components tapioca starch, arabic gum (E-414) and triacetine)
Edible glue used to attach the lozenge to the handle - dextrates hydrated, maize starch and purified water
Printing ink – ethanol, water, purified shellac (E904), acetone, FD&C Blue No.1 (E133 Brilliant Blue FCF) and ammonium hydroxide (E527).

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%). No polymorphic forms are described and the drug substance does not change its crystal form after milling or blending.

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.

<u>Manufacturing process</u>
CEPs have 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. with additional requirements for particle size distribution and microbial purity. 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 60 months (both manufacturers) 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. The choice of excipients is justified and their functions explained. Compatibility studies of the drug substance and the excipients have been performed and some incompatibilities with citric acid have been observed in the initial studies, which were not confirmed in the more detailed analyses.
Comparative dissolution data has been provided on the test and reference product. In support of the biowaiver of strengths, the 200, 600, 800, 1200 and 1600 microgram were compared to the 400 microgram strength at the investigated pH experimental conditions of 1.2, 4.5, 6.8 and 7.4 (oral cavity) and rotation speed 50, either directly via one unit only of both strengths comparison or via same dose comparison. In all these cases the lower limit of the 90% confidence interval for the f2 similarity factor via bootstrapping was above 50. One exception was noted, but sufficiently explained and accepted. Overall, the pharmaceutical development is acceptable.

Manufacturing process
The manufacturing process consists of mixing and compression and has been validated according to relevant European guidelines. The applicator is attached using edible glue. The process is considered a non-standard process as the unit dose contains less than 2% active substance. Process validation data on the product have been presented for a sufficient number of batches for lowest and highest strength (200 and 1600 microgram) in accordance with the relevant European guidelines.

Control of excipients
Disodium phosphate anhydrous, magnesium stearate and citric acid anhydrous meet the specifications of the current Ph.Eur. The dextrates comply with the United States Pharmacopeia requirements. In-house specifications are listed for the berry flavour, ink and applicator. 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, dissolution, assay, degradation products, uniformity of dosage units, hardness, and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for assay which is wider at shelf-life and for appearance (which allows the appearance of brown spots). The specification is considered acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data for all strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of the 200 microgram strength, one batch of 800 microgram strength and three batches of 1600 microgram strength stored at 25°C/60% RH (up to 36 months), 30°/65% RH (up to 12 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-PCTFE-PVdC-PVC/Al blisters. On basis of the data submitted, a shelf life was granted of 36 months. The proposed storage condition of '*Store below 25 °C*' is also acceptable.

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 CF 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 CF is intended for hybrid 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 hybrid 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.

For this hybrid application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fentanyl CF 400 microgram, lozenges with integral applicator for oromucosal use (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Actiq 400 microgram, lozenges with integral applicator for oromucosal use (Teva Pharma B.V., NL).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference product. Actiq is a hybrid dossier with the same pharmaceutical form and strengths as applied for here.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Biowaiver</u>
The adequacy of waiving additional *in vivo* bioequivalence testing for the additional strengths (i.e., 200, 600, 800, 1200 and 1600 microgram) is thus supported, given that the general requirements laid down in the EMA Guideline on Bioequivalence for such purpose are met. Concretely:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths can be considered as quantitatively proportional, given that the amount of the API is <5 % of the core weight, and that only the amount of the filler (dextrates) is changed to account for the change in amount of drug substance, whereas the amounts of other core excipients are the same for the concerned strengths.
d) dissolution profiles may be accepted as similar without further mathematical evaluation since more than 85% of the drug is dissolved within 15 minutes.

In conclusion, the results of the bioequivalence study can be extrapolated to the other strengths. The MAH has fulfilled all conditions for a biowaiver of strengths.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 37 healthy subjects, aged 18-37 years. Each subject received a single dose (400 microgram) of one of the 2 fentanyl citrate formulations. The researcher controlled this administration, giving instructions to the volunteer (as done during the training session) to move the tablet around inside the mouth with the aid of the applicator in order to maximize the mucosa area exposed to the product. The volunteer was reminded to suck on the lozenge and not to chew it, attempting to consume it during the next 15 minutes. In addition, on two occasions they received three doses of the antidote: 50 mg of naltrexone 12 hours before, immediately before and 12 hours after each one of the administrations of fentanyl. The volunteers also received naltrexone, three doses in each one of the two periods. One of the doses of naltrexone was administered 12 hours before fentanyl administration, the second dose was administered right before administration of fentanyl and the third dose was administered 12 hours after fentanyl administration. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0, 5, 10, 15, 20, 30, 40, 50, 60 minutes and 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Fasting conditions are adequate, as the product may be taken regardless of the food intake.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 36 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of fentanyl under fasted conditions.

Treatment N=36	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	3920 ± 1715	4571 ± 1904	815 ± 295	0.67 (0.33-2.00)
Reference	3679 ± 1649	4349 ± 1901	782 ± 252	0.83 (0.33-2.00)
***Ratio (90% CI)**	1.06 (0.97 – 1.15)	1.05 (0.97 – 1.14)	1.03 (0.92 – 1.15)	--
CV (%)	1.06 (0.98 – 1.14)	1.05 (0.98 – 1.12)	1.03 (0.93 – 1.13)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fentanyl CF is considered bioequivalent with Actiq.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 CF.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug abuse
	• Drug diversion
	• Pharmacodependence
	• Drug misuse
	  o Incorrect/no titration
	• Off-label use including:
	  o Use in cancer patients who are not already receiving opioid maintenance therapy for chronic cancer pain
	  o Use in non-cancer acute or

	chronic pain • Accidental exposure • Medication errors • Overdose • Respiratory depression • Local tolerability o Including dental disorders (especially as the lozenges contain sugar)
Important potential risks	• Cardiovascular/circulatory depression • Anaphylaxis • Occurrence of brain lesions in form of multifocal neuronal mineralisation/necrosis following repeated application of high doses of fentanyl in rats (relevance to human is unknown) • Drug interaction with serotonergic syndrome
Missing information	• Pregnant, breastfeeding women • Paediatric population • Patients with renal or hepatic dysfunction • Long-term use

The MAH committed to additional risk minimisation measures including educational material. The educational material should contain the following key elements:

- Prescription of the product only by physicians experienced in the management of opioid therapy in cancer patients
- Prescription of the product only to critically selected patients with close following on instructions for use, instructions on opening, information on indication and risk of abuse, information on the titration process
- Instruction on safe use, storage and disposal

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the product Actiq. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid 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: a pilot test with 2 participants, followed by 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 CF 200 microgram, 400 microgram, 600 microgram, 800 microgram, 1200 microgram and 1600 microgram, lozenges with integral applicator for oromucosal use have a proven chemical-pharmaceutical quality and are hybrid forms of Sublimaze 50 mcg/ml solution for injection. Sublimaze is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 January 2019.

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