LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fentasub 67 µg, 133 µg, 267 µg, 400 µg, 533 µg and 800 µg sublingual tablets
Fentanyl citrate

SE/H/1315/01-06/DC

This module reflects the scientific discussion for the approval of Fentasub. The procedure was finalised at 2013-09-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Fentasub 67, 133, 267, 400, 533, 800 microgram, sublingual tablets, are hybrid applications made according to Article 10(3) of Directive 2001/83/EC. The applicant Ethypharm applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as CMS.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is originator product Sublimaze, 50 micrograms/ml, solution for injection authorised in UK since 1980, with Jansen-Cilag Ltd as marketing authorisation holder. The reference product used in the bio-equivalence studies is Actiq, compressed lozenges marketed by Cephalon UK Ltd in UK and FR.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Fentasub is presented in the form of sublingual tablets containing 110 micrograms, 210 micrograms, 420 micrograms, 630 micrograms, 840 micrograms and 1260 micrograms, respectively, of fentanyl citrate which corresponds to 67 micrograms, 133 micrograms, 267 micrograms, 400 micrograms, 533 micrograms and 800 micrograms, respectively, of fentanyl. The excipients are calcium hydrogen phosphate anhydrous, cellulose microcrystalline, magnesium stearate, hypromellose, disodium phosphate anhydrous, macrogol, maltodextrin, titanium dioxide, triacetin, and printing ink containing shellac and black iron oxide. The sublingual tablets are packed in peelable child-resistant blisters:

- Polyamide-Aluminium-PVC / Aluminium foil blister
- Polyamide-Aluminium-PVC / Aluminium-PET foil blister

II.2 Drug Substance

Fentanyl citrate has a monograph in the Ph Eur.

Fentanyl citrate is a fine white to off-white, crystalline powder which is soluble in water, freely soluble in methanol and sparingly soluble in ethanol (96 per cent).

The manufacturer holds a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM). This certificate verifies that the substance is suitably controlled by the monograph “Fentanyl citrate” no. 1103 published in the European Pharmacopeia. The methods used for analysis of the drug substance are those described in the monograph.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Fentasub sublingual tablets are formulated using excipients described in the current Ph Eur, except for the ready to use coating mixture and printing ink, which are controlled according to acceptable in house specifications. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in the original package in order to protect from light.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetic documentation consists of two bioequivalence studies comparing Fentasub with Actiq lozenges and one dose-proportionality study. All studies were single-dose studies conducted in healthy volunteers under fasting conditions.

After single-dose administration of Fentasub quantifiable fentanyl concentrations in plasma is seen after 10-20 min. Mean maximal plasma concentrations of fentanyl are reached after 50 to 90 min. Dose-proportionality over the dose range of 133-800 µg has been demonstrated.

Fentasub is suprabioavailable compared to Actiq, with an AUC-ratio of 1.5:1. Bioequivalence between Fentasub 800 µg and Actiq 1200 µg and between Fentasub 133 µg and Actiq 200 µg has been demonstrated for AUC_{0-t} and C_{max}. However, the early exposure (measured as AUC up to 2h) was about 30-50% higher for Fentasub and t_{max} was shorter compared to Actiq (50-90 min vs. 2h). See Figure 1 and Figure 2 below.

Figure 1: Mean plasma profiles: Fentanyl 800 µg sublingual tablet *versus* Actiq® 1200 µg (N=41).

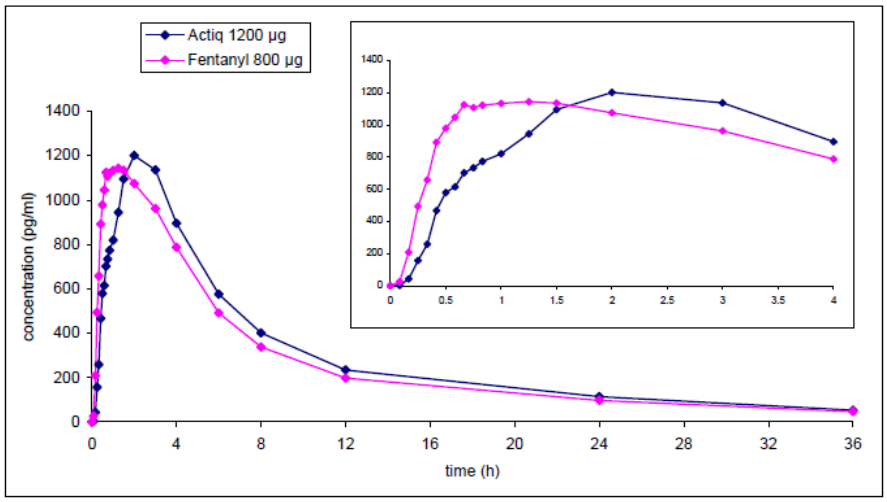
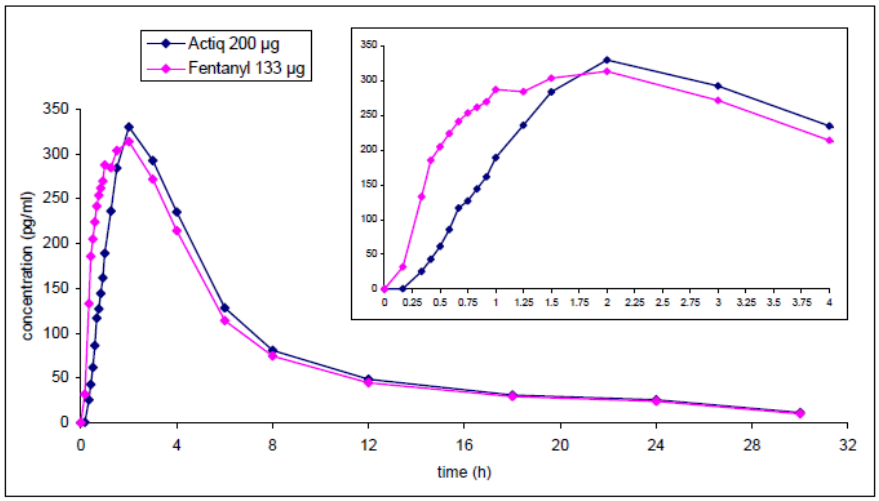


Figure 2: Mean plasma profiles: Fentanyl 133 µg sublingual tablet *versus* Actiq® 200 µg (N=40).



In vitro and *in vivo* data suggest a 30 minute dwell time to be sufficient to reach an exposure similar to Actiq. Hence, the SmPC statement that the tablet can be swallowed after 30 minutes, if remnants from the tablet remain is accepted.

The pharmacokinetics of this new fentanyl formulation has been satisfactorily characterised.

IV.2 Discussion on the clinical aspects

The Applicant supports the efficacy and safety of the product with the results of the pharmacokinetic studies, one clinical efficacy study and published data.

The present RMS has earlier acted as RMS for similar products and has had the opinion that from the available non-protected efficacy and safety data for fentanyl (e.g. Actiq) it is possible and also sufficient to estimate the efficacy and safety of new fentanyl products based only on acceptable pharmacokinetic data.

The quality of the submitted pharmacokinetic data is assessed as good. There is a consistency within the results from two pharmacokinetic studies. C_{max} is similar between Actiq and Fentasub and the T_{max} is shorter which is desirable is cases of breakthrough pain.
Each patient must be titrated to an optimal dose. The intra-individual variation is low.
Fentasub has demonstrated dose proportional pharmacokinetics over the dose range of 133-800 µg, after single dose administration.

With these conditions fulfilled, the RMS has the opinion that additional clinical efficacy and safety studies are not necessary for an approval of the product. With the demonstrated similar pharmacokinetic profiles the efficacy and safety predictability for Fentasub should be at least as good as for Actiq.

During the procedure and in response to questions raised by CMS, the results from a Phase III study (randomized, double-blind, placebo-controlled, cross over design) "Randomized, placebo-controlled study of Fentanyl Ethypharm for breakthrough pain in opioid-treated patients with cancer" (Clinical Study Report FYL/24019/008) have been presented as support for clinical efficacy. The Sum of Pain Intensity Differences at 30 minutes was significantly greater for breakthrough pain episodes treated with fentanyl compared with those treated with placebo.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A reference regarding content and layout is made to the duplicate reference product Fentanyl Ethypharm. The Fentanyl Ethypharm PIL was user tested and approved during procedure SE/H/1177/01-06/DC. This reference is considered acceptable.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of bioequivalence.

The risk/benefit ratio is considered positive and Fentasub 67 µg, 133 µg, 267 µg, 400 µg, 533 µg and 800 µg sublingual tablets is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Fentasub 67 µg, 133 µg, 267 µg, 400 µg, 533 µg and 800 µg sublingual tablets was successfully finalised on 2013-09-26.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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