LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fentanyl Ethypharm, 67, 133, 267, 400, 533, 800 mikrogram, Resoriblett, sublingual (fentanyl citrate)

SE/H/1177/01-06/DC

This module reflects the scientific discussion for the approval of Fentanyl Ethypharm. The procedure was finalised at 2012-10-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Ethypharm has applied for a marketing authorisation for Fentanyl Ethypharm 67, 133, 267, 400, 533 or 800 microgram sublingual tablets claiming essential similarity to Sublimaze 50 microgram/ml solution for injection marketed in Sweden by Jansen-Cilag. The product contains fentanyl as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence studies is Actiq, compressed lozenges marketed by Cephalon UK Ltd in UK and FR.

II. QUALITY ASPECTS

II.1 Introduction

Fentanyl Ethypharm 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 aluminium – aluminium blisters.

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

Fentanyl Ethypharm sublingual tablets is 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 Fentanyl Ethypharm 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 Fentanyl Ethypharm 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.

Fentanyl Ethypharm is suprabioavailable compared to Actiq, with an AUC-ratio of 1.5:1. Similar bioavailability between Fentanyl Ethypharm 800 µg and Actiq 1200 µg and between Fentanyl Ethypharm 133 µg and Actiq 200 µg has been shown for AUC_{0-t} and C_{max}. However, the early exposure (measured as AUC up to 2h) was about 30-50% higher for Fentanyl Ethypharm 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).

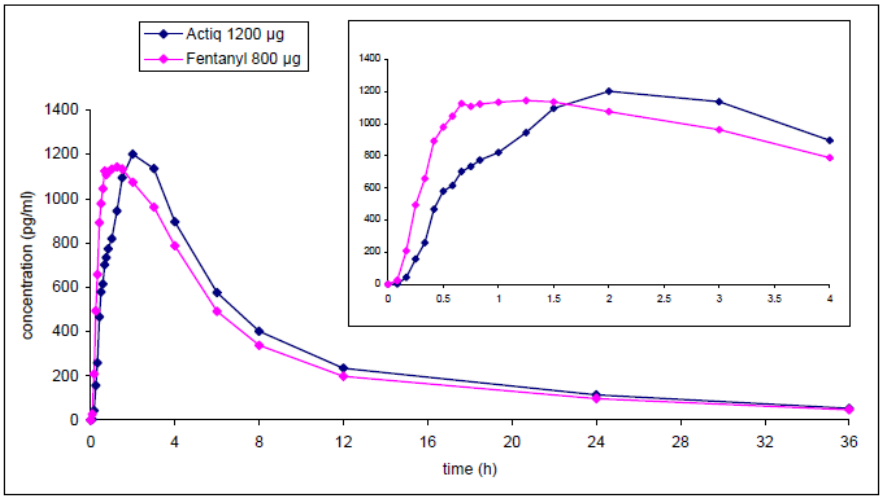
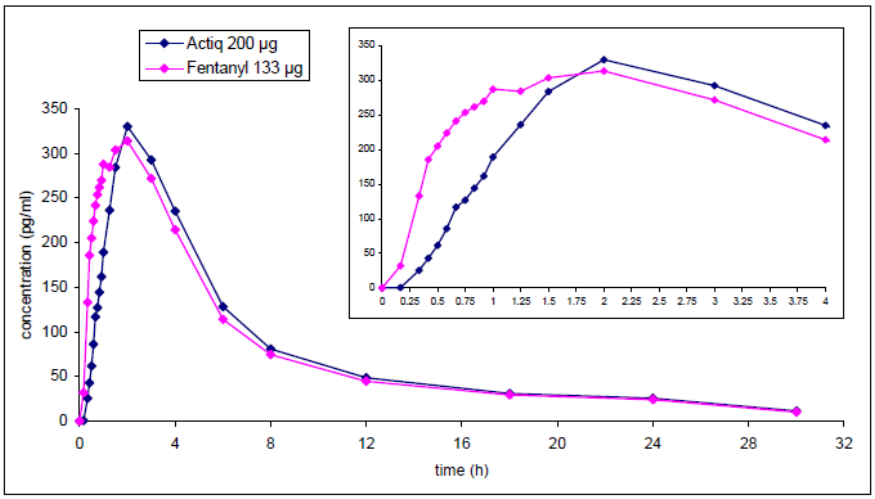


Figure 2: Mean plasma profiles: Fentanyl 133 µg sublingual tablet *versus* Actiq® 200 µg (N=40).



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.

Clinical efficacy

The Applicant bases the efficacy and safety of the product with the results of the pharmacokinetic studies and on published data. No clinical efficacy studies have been performed for Fentanyl Ethypharm.

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 for the two pharmacokinetic studies. C_{max} is similar between Actiq and Fentanyl Ethypharm and the T_{max} is shorter which is desirable is cases of breakthrough pain. Each patient must be titrated to an optimal dose. The intraindividual variation is low. Fentanyl Ethypharm has demonstrated doseproportional pharmacokinetics over the dose range of 133-800 µg, after single dose administration.
With these conditions fulfilled, the RMS has the opinion that any clinical efficacy and safety studies are not necessary for an approval of the product. With the shown similar pharmacokinetic profiles the efficacy and safety predictability for Fentanyl Ethypharm should be at least as good as for Actiq.

IV.2 Discussion on the 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 clinical efficacy/safety data, no further such data have been submitted or are considered necessary

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet 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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet 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.

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 Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Fentanyl Ethypharm 67, 133, 267, 400, 533 or 800 microgram sublingual tablets is recommended for approval.

VI. APPROVAL

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The Decentralised procedure for Fentanyl Ethypharm 67, 133, 267, 400, 533 or 800 microgram sublingual tablets were successfully finalised on 2012-10-01.

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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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