Decentralised Procedure

Public Assessment report

Fentavera 12/25/50/75/100 µg/h transdermal patches

Fentanyl

DE/H/1449/001-005/DC

Applicant: Acino Pharma GmbH

Reference Member State	DE
Date of this report:	11.09.2009

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Fentavera 12/25/50/75/100 µg/h
INN (or common name) of the active substance(s):	Fentanyl
Pharmaco-therapeutic group (ATC Code):	N02 AB03
Pharmaceutical form(s) and strength(s):	Transdermal patches with 12/25 / 50 / 75 / 100 µg/h
Reference Number for the Decentralised Procedure	DE/H/1449/01-05/DC
Reference Member State:	Germany
Member States concerned:	ES/PL/UK
Applicant (name and address)	Acino Pharma GmbH, Am Windfeld 35 DE-83714 Miesbach
Names and addresses of manufacturers responsible for batch release in the EEA	Acino Pharma GmbH, Am Windfeld 35 DE-83714 Miesbach

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Fentavera 12/ 25 / 50 / 75 / 100 µg/h, in the treatment of chronic pain which can only be treated adequately and effectively with opioid-analgetics, is approved.

II EXECUTIVE SUMMARY

II.1 Problem statement

This application is submitted in accordance with Article 10.1 of Directive 2001/83/EC. The originator product is Durogesic 12 - 100 µg/h, marketing authorisation holder Janssen-Cilag, Neuss, Germany. The products under discussion are generic to the originator products already marketed in several European countries.

II.2 About the product

Fentanyl is a synthetic opioid analgesic, belonging to the piperidine derivatives, and is chemically related to pethidine. Fentanyl is 75-100 times more potent than parenteral morphine. The analgesic and sedative action of fentanyl is proposed to be mediated mainly through µ-opioid-receptors. Fentanyl has been marketed as iv anaesthetic since the 1960s. Today fentanyl is extensively used as an anaesthetic and analgesic. Fentanyl has a high lipid solubility which makes it suitable for transdermal administration.

The transdermal fentanyl patch technology has been used clinically to provide analgesia since 1991. In general, transdermal patches are flexible pharmaceutical preparations of varying sizes, containing one or more active substances. Transdermal patches should be applied to intact skin in order to deliver at a constant rate the active substance to the systemic circulation. Once the patch is applied to the skin the drug diffuses in the subcutaneous tissues and forms a reservoir. Therefore, the elimination half-life is longer compared to other administration routes, with about 17 h for fentanyl after transdermal administration, compared to parenteral and transmucosal administered drug of 7 h. The release of the drug from the patch is controlled without membrane. The rate controlling step of drug absorption is commonly the release from patch matrix and the permeation through the skin.

II.3 General comments on the submitted dossier

The submitted dossier is of good quality.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product inside and outside the EU.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II.5 Pharmacovigilance System / Risk Management Plan

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The raw drug substance can be described as a white to almost white powder, practically insoluble in water, freely soluble in alcohol and in methanol.

Fentanyl is supplied by two different manufacturers.
The quality of the drug substance fentanyl is controlled in compliance with the monograph of the European Pharmacopoiea (Ph.Eur.). The suitability of the monograph to test the drug substance has been verified by Active Substance Master Files or CEP.

The specifications in the ASMFs were satisfactory and met the requirements of Ph.Eur.. The impurities/degradation products were classified and analysed appropriately. The potential impurities/degradation products were limited according to the monograph of the European Pharmacopoeia. The re-test period of two years is acceptable.

Drug Product

The ingredients and the manufacturing process of the drug product are in general considered suitable to produce a pharmaceutical product of the proposed quality.
As required in Directive 2001/83/EC, the documentation provides an adequate synopsis of the method of preparation, mentioning the various stages of production, the in-process controls and batch formula.

The manufacturing processes demonstrated the consistency of the specifications. The process has been validated adequately by investigating the critical manufacturing steps.

The excipients are appropriately controlled, using either Ph. Eur. Monographs or in-house testing. Satisfactory supplier Certificates and Certificates of Analysis are supplied.

The stability data presently available (12 months for the product proposed for marketing and 30 months for supportive batches) justifies a claimed shelf-life of 24 months if stored in the package proposed for marketing.

III.2 Nonclinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of (transdermal) fentanyl hydrochloride are well known, so no further non-clinical studies are required.

The possible risk of phototoxicity has been adequately discussed by the applicant. Hence, in agreement with current guidance on photosafety testing (CPMP/SWP/398/01) and the European directive 2000/33/EC, no photoreactive potential can be expected.

The transdermal fentanyl system of the application differs in its excipients from the reference product Durogesic of Janssen-Cilag. Therefore, local tolerability of the patch was the main concern of the non-clinical safety evaluation. The adhesive and the tackifier of the patch have also been used in other approved medicinal products. Moreover, the applicant included a report from a dermal irritation assessment of the adhesive in rabbits. In addition, two preclinical studies analysing the skin sensitisation properties of the present fentanyl transdermal system, of the tackifier and the smoothener Aloe vera leaf extract oil were performed in guinea pigs according to the Buehler method as recommended in the OECD guideline 406 and the European directive 96/54/EC. The results from all these studies do not indicate any significant skin irritation or sensitisation potential.

There are no non-clinical objections to approval of Fentavera transdermal patches.

III.3 Clinical aspects

The application is an abridged dossier. This is appropriate in the case of a generic synonym product. Fentanyl is well known, and in case of a synonym product containing a widely used, well-known active substance, no further clinical trials are required and none are provided by the applicant.

Dose linearity in fentanyl release has been demonstrated for the different patch sizes. Therefore data obtained by studies conducted with one dose can be extrapolated to other proposed patch sizes, provided that the same amount of fentanyl per cm^2 of patch surface is granted. All six strengths of Fentavera ensure this condition.
As a conclusion extrapolation of the pharmacokinetic data of Fentavera 25µg/h, to the other patch strengths is acceptable.

To support the application, the applicant has submitted a combined single dose/multiple dose and additionally one single dose and two multiple dose studies(with a different patch size)

The relevant study demonstrated bioequivalence of the applied product ”Fentavera ” with the originator product, i.e. Durogesic SMAT®.(marketed in Germany)

IV BENEFIT RISK ASSESSMENT

The application contains an adequate documentation of the safety, quality and pharmaceutical development program.

The pharmacokinetic data presented are sufficient to demonstrate interchangeability of the generic and originator product with regard to safety and efficacy.