DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

SUMMARY OF CLINICAL AND BIOPHARMACEUTICS REVIEW OF STUDIES SUBMITTED IN RESPONSE TO A PEDIATRIC WRITTEN REQUEST

Application	NDA 20-747/027
Applicant	Cephalon, Inc.
Drug name	Actiq (Oral Transmucosal Fentanyl Citrate)
Route	Oral transmucosal

Table of Contents

Background

Actiq (oral transmucosal fentanyl citrate) was approved on November 4, 1998 for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. On April 30, 2003, Cephalon submitted a Proposed Pediatric Study Request to IND 27,428 for Actiq in order to obtain a Pediatric Written Request (PWR) and qualify for pediatric exclusivity.

A PWR was issued on December 23, 2003 (PWR#1) to obtain needed pediatric information on dosing, pharmacokinetic parameters, effectiveness and safety of fentanyl citrate in pediatric cancer patients receiving around-the-clock opioids and requiring additional opioid therapy for breakthrough pain (BTP). The PWR included a request for a randomized, double-blind, placebo-controlled, fixed-dose trial with the following objectives:

1. Determine the minimum safe and effective starting dose for oral transmucosal fentanyl citrate (OTFC)
2. Characterize the PK of OTFC
3. Establish a safe and effective titration scheme for OTFC
4. Obtain data to investigate the exposure and efficacy relationship between plasma concentrations of fentanyl and clinical measures of analgesia.

The trial, using the approved ACTIQ formulation, was to be carried out in opioid-tolerant pediatric patients between the ages of 3 and 16 years. A sufficient number of patients to provide at least 80% power to detect a statistically significant difference in the primary efficacy endpoint were to have completed the study. The patients were to have been approximately equally distributed across the age groups (and within the age ranges 3- <6 years, 6-<11 years, and 11-16 years). A minimum of six patients were required for each age group to complete the PK portion of the study. A minimum of 10 evaluable patients were required for each age group in order to characterize the safety of the drug. The applicant determined that in order to meet the estimated power calculation of 80% for the efficacy assessment, 38 patients were required to complete the double-blind study.

The study population as per the first written request was to have been comprised of opioid-tolerant pediatric patients with BTP due to cancer. However, due to difficulty in recruitment (according to the applicant because of a limited number of patients available to meet the inclusion criteria of the protocol, and parents' reluctance to enroll their seriously ill pediatric patients in a placebo-controlled trial), the population was expanded to include opioid-tolerant pediatric patients with BTP for any reason (e.g. sickle-cell disease, burns, injuries) in addition to cancer. In consultation with the Pediatric Implementation Team (PDIT), the division determined that efficacy findings from this broader study population could be applied to the intended population of pediatric patients with cancer.

In addition to the amendment to the original written request which broadened the study population to include cancer and non-cancer patients, the timeframe for submitting the study reports was extended three times (in order to allow additional time for patient enrollment). PWR #2 was issued on November 9, 2005, and PWR #3 on July 13, 2006.

The following table illustrates the history of the written request for Actiq.

Table 1: History of the ACTIQ® PWR

Date	Applicant Action	Agency Action
4/30/03	**PPSR submitted**	
7/28/03	**Protocol submitted and study initiated:** C8278b/202/BP/US-CA "A Double-Blind, Placebo-Comparison Study to Evaluate the Efficacy and Safety of ACTIQ® Treatment for Children and Adolescents with Cancer and Breakthrough Pain"	
12/23/03		**PWR # 1 issued**
5/5/04	**Formal Dispute Resolution Request:** Applicant sought to replace the requested double-blind, placebo-controlled efficacy study with studies that characterized the safety, tolerability, and pharmacokinetics, "with or without an open label evaluation of efficacy".	**Agency response on 6/4/04:** uncontrolled efficacy data not acceptable
9/29/04	**Protocol submitted:** C8278/2022/BP/US-CA "A 4-Week, Open-Label Extension Study of ACTIQ® (Oral Transmucosal Fentanyl Citrate [OTFC®]) Treatment for Children and Adolescents with Cancer and Breakthrough Pain"	
10/26/04		**Amendment to PWR #1** extended timeframe for submission of study reports from 3/5/2005 to 4/5/2005
9/1/05	Only 4 patients enrolled in double-blind study	
4/20/05	**Request** that study population be expanded to include opioid-tolerant pediatric patients with BTP caused by conditions other than cancer (e.g. burns, sickle cell disease), to increase enrollment	
11/9/05		**PWR # 2 issued** • Expanded population to include cancer and non-cancer patients • 1/3 patients completing study must be cancer patients • Extended timeframe for submission of study reports to 5/31/05
3/6/06	**Request** • extension of timeframe for submitting study reports • remove minimum number of patients per age group	

Date	Applicant Action	Agency Action
	• amend PK section to clarify timing of PK blood samples	
7/13/06		**PWR # 3 issued** • Extended timeframe for submission of study reports to 9/4/06 • Clarified timing of PK/PD time points for obtaining blood samples • **Minimum number of patients not removed**
9/1/06	**Study reports submitted to Agency**	

The final trial design was a 3-phase study (Phases A, B, and C) that evaluated the efficacy and safety of individually titrated ACTIQ treatment in hospitalized opioid-tolerant pediatric patients who were receiving ATC opioid medication for pain a minimum of seven days and who required additional medication for BTP. Phase A consisted of open-label titration to determine the optimal dose of ACTIQ; Phase B consisted of blood sampling for drug assay and efficacy measurements for one unit of optimal-dose ACTIQ; and Phase C consisted of a double-blind, placebo comparison evaluating the management of four BTP episodes, with the child treated with either the optimal ACTIQ dose (3 BTP episodes) or a placebo (1 BTP episode).

The chosen primary endpoint for the double-blind trial was pain intensity difference 15 minutes (PID_{15}) after initiation of each Actiq dose during the double-blind phase of the trial. Pain intensity was measured using the Faces Pain Scale-Revised (FPS-R).

To minimize the potential harm to pediatric patients from unmanaged pain, this study included provision for early administration of rescue medication and limited the use of placebo treatment to one of four episodes of BTP, in contrast to three of ten episodes as was done in the study of adult patients.

The open-label extension of the study (study 2022) further evaluated ACTIQ treatment in pediatric patients who successfully completed the double-blind study and elected to enroll in the open-label study. Pediatric patients may have been either inpatients or outpatients for the open-label study.

Efficacy

Eleven (of 38 planned) patients completed Phase C of the trial. There was no statistically significant difference between Actiq and placebo treatment for the primary efficacy variable of PID 15 minutes after the start of study drug administration or for any of the secondary efficacy variables as related to pain intensity (PI), time to and duration of analgesia, over-sedation, or rescue medication use.

The data obtained from this trial (202) was insufficient to support the efficacy of Actiq use in opioid-tolerant pediatric patients with BTP secondary to cancer. Sufficient statistical power for efficacy analyses was not obtained with data collected on the small number of evaluable patients. Given the small sample size and the lack of power, no definitive conclusions can be made in regard to the primary efficacy variable, PID 15 minutes after study drug administration, or the secondary efficacy variables examined in the double-blind study.

Safety

The safety database consisted of 15 patients; two aged three to < six, three aged six to < eleven, and ten aged eleven to <sixteen. The written request required at least ten patients in each age group be evaluated.

Pediatric patients participating in these studies (202 and 2022) used only the lower ACTIQ doses, i.e., 200, 400, and 600 mcg. No deaths, withdrawals due to adverse events, or treatment-related serious adverse events occurred in these studies. No unexpected adverse events occurred.

Given this patient population, there were no unexpected findings in clinical laboratory values, vital signs values, ECG findings, physical examination findings, SpO2 levels, or sedation. The interpretation of these data, however, is limited because of the small number of patients.

Clinical Pharmacology and Biopharmaceutics

During the open-label phase of the study (phase B), fentanyl plasma concentrations were obtained in 12 pediatric and adolescent patients prior to dosing and at 15, 30, 45, 60, 120, 180, 360, and 480 minutes after dosing. These data were analyzed using both noncompartmental and compartmental methods. A two-compartment model with first-order absorption and elimination described the time course of fentanyl concentrations. Both analysis methods gave comparable estimates of fentanyl exposure.

Exposure-response was evaluated using the fentanyl plasma concentrations and corresponding PI scores obtained in phase B. There was a trend for the pain intensity difference to increase with increasing fentanyl exposure (as measured by both concentration at 15 min and model-predicted Cmax). However, the major limitation with this analysis is the graphs do not take into account a placebo response which was observed in the double-blind Phase C of the study.

The data and population pharmacokinetic model describing fentanyl pharmacokinetics in pediatric and adolescents are acceptable. Therefore, we recommend updating the current label with a description of the pharmacokinetic parameters.

Conclusions and Recommendations

1. The supplement is approved for labeling changes. Language regarding the pharmacokinetics of Actiq in opioid-tolerant pediatric and adolescent patients has been added to the Pediatric Use section of the label.
2. The Applicant has not fulfilled the requirements of the Pediatric Written Request.
3. Pediatric exclusivity has been denied as per the Pediatric Exclusivity Board memo of November 27, 2006

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/s/

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2/6/2007 05:09:49 PM
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I concur.