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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

MEMORANDUM

DATE: April 26, 2008

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the May 6, 2008 ALSDAC Meeting to Discuss Supplement 005 to NDA 21-947 for an Expanded Indication for Fentora for Use in Break-Through Pain in Patients with Chronic Pain Not Caused by Malignancy

Fentora was approved in 2006 for the treatment of breakthrough pain in patients with cancer who are already treated with around-the-clock opioids. Actiq, approved for the same indication in 1998, was the first oral transmucosal fentanyl product developed for this indication. Actiq is a lozenge that is presented on a stick making it easily removable from the mouth, while Fentora is a lozenge without a stick. Because approval of these products represented availability of fentanyl without the necessity of intravenous access, FDA had numerous discussions with the sponsors during the development of the products to address our concerns regarding the potential for abuse and misuse, and the potential for accidental exposure with these formulations. In order to prevent abuse and misuse, and accidental exposure to Actiq and Fentora, particularly by children, rigorous risk management programs were included as part of the approval of the products. These risk management plans were designed to limit the prescribing of these products to opioid-tolerant patients with breakthrough pain from cancer with the intent that this would limit the overall prescribing of the medication and, perhaps, limit the amount of diversion for abuse, and the number of accidental exposures. However, off-label prescribing has, unfortunately, been widely practiced. In the short time that Fentora has been on the market, and despite a limited indication for cancer patients, we have received numerous

reports of serious adverse events related to the product, including deaths in patients, prescribing to non-opioid tolerant patients, misunderstanding of dosing instructions, and inappropriate substitution of Fentora for Actiq by pharmacists and prescribers. The Agency issued a Public Health Advisory regarding Fentora last September. Additionally, we worked with the sponsor to make a number of modifications to strengthen the warnings in the product label.

While there are patients with chronic, non-cancer breakthrough pain who may benefit from Fentora or similar products, controversy exists in the literature regarding the extent of this population and the safety and efficacy of these types of products for these patients. It is difficult at best to fully assess whether to expand the indication based on this literature. While the prescribing of Actiq, and more recently Fentora, has remained at relatively low levels, we are concerned that the sponsor's request to expand the current indication for Fentora to opioid tolerant patients with breakthrough pain who do not have cancer may greatly increase the prescribing of this product which may increase the availability of the product for diversion, abuse and misuse, and increase the incidence of accidental exposures which, due to the potency of the product, could potentially have devastating effects. In this time of increasing abuse of prescription opioid products, it is important to address this potential and to find effective risk mitigation strategies to intervene before it manifests as a public health crisis.

Fentanyl has an extremely narrow therapeutic window, and even in opioid tolerant patients misuse and errors in dosing can result in significant morbidity and mortality. Exposure to minute quantities of fentanyl in opioid non-tolerant people, especially children and the elderly, can be lethal in minutes. If this product is to be indicated for increased widespread use, and if availability increases, a risk mitigation program that will attempt to prevent, monitor and intervene when necessary will be essential. However, as already noted, the current paradigms for risk management programs for potent opioid drug products may not have been fully successful.

During this meeting of the ALSDAC, we will be asking you to help us determine the safety and efficacy of this expanded indication for Fentora. Should you conclude that there is, indeed, an appropriate patient population for this indication, we will ask for your assistance in creating new and effective risk mitigation strategies to prevent misuse, abuse and diversion of this highly potent opioid product. These are difficult questions and we are extremely grateful that you have agreed to participate in this discussion and to attempt to provide recommendations that will be critical in our determination regarding the approvability of this application. Thank you in advance for your participation.

Background
Transmucosal Fentanyl
Approval History

The first formulation of oral transmucosal fentanyl citrate to be approved was Oralet. It was approved in 1993 for preoperative sedation in children, and was for use only in a hospital setting in an effort to avoid serious hazards associated with off-label use. The product was formulated as a raspberry flavored lozenge on a stick so that it would be acceptable to the pediatric population. However, Oralet was withdrawn from the market when it became evident that the opioid-naïve children who received it could not tolerate the associated adverse events of nausea and vomiting.

In November 1998, Actiq was approved for a novel indication; the treatment 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. The approval process for Actiq brought to light a situation where the need for a new therapy for cancer breakthrough pain had to be balanced with the management of the potential public risk associated with the marketing of a potent narcotic. This represented a unique circumstance where the population at greatest risk for adverse effects was not the population that would benefit from approval. Actiq was the same formulation as Oralet, a raspberry flavored lozenge on a stick, but was available in doses much higher than approved for Oralet. In contrast to Oralet, Actiq was intended for use in the home and there was great concern about the appeal of this dosage to children in the household.

This matter was the subject of an ALSDAC meeting in September of 1997. The committee voted unanimously that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health. While the risks related to the approval of Actiq and its use in an outpatient setting included those common to all high-potency opioids including misuse (particularly in opioid-naïve patients), abuse, and diversion, a very important and unique risk stood out; the accidental or intentional ingestion of the product by children who have mistaken the lollipop formulation for candy. The issue of partially consumed units left lying around the house was of particular concern to the Agency.

The Agency issued a Nonapproval Action for Actiq in November, 1997, based partly upon the lack of development of an adequate program to protect the safety of those individuals who may accidentally or intentionally ingest the product by mistaking it for candy, use it illicitly, or have it inappropriately prescribed off-label. Actiq was ultimately approved in 1998 under 21CFR§314.20 (Subpart H) "Approval with restriction to assure safe use" which states:

"If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product"

The Agency approved the NDA with restriction for use to the treatment of breakthrough pain associated with malignancy in opioid-tolerant cancer patients (also limiting pharmaceutical marketing detailing to Oncology and Pain Medicine specialists) and with the final printed labeling and Risk Management Program as a condition of approval.

The regulations under which this product was approved provide for accelerated withdrawal of the product if the Sponsor does not adhere to the agreed upon marketing restrictions.

There have been several labeling changes for Actiq since the time of approval. Those of significance include the addition of a statement advising diabetic patients that Actiq contains two grams of sugar per unit (June 10, 2002); statements added to label based on post-marketing experience regarding the association of Actiq with dental caries, tooth loss, and gum line erosion (September 24, 2004); formulation change to sugar-free (never marketed, September 9, 2005); conversion of patient leaflet (patient package insert) to MedGuide (September 6, 2006); and the addition of pharmacokinetic data for patients 5-15 years of age based on a study carried out in the pediatric population (February 7, 2007).

Fentora was approved for the treatment of cancer breakthrough pain on September 25, 2006. Both a Risk Management Plan and MedGuide were part of the approval. The originally approved dosage units of Fentora included 100, 200, 400, 600, and 800mcg, and in March, 2007, a 300mcg strength was approved.

The table below, excerpted from the currently approved Fentora label, illustrates the difference in bioavailability between Actiq and Fentora. Because of the almost 30% difference in their bioavailability, caution must be exercised in converting patients to Fentora from Actiq. Since the two products have some dosage units in common (200, 400, 600, 800 mcg), and are comprised of the same drug moiety, it is crucial that prescribers and pharmacists understand this difference.

Table 1. Pharmacokinetic Parameters* in Adult Subjects Receiving *FENTORA* or Actiq

Pharmacokinetic Parameter (mean)	*FENTORA* 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
AUC_{0-tmax} (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05
AUC_{0-inf} (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
***Actiq data was dose adjusted (800 mcg to 400 mcg).

Within a year of its approval, in September 2007, a Public Health Advisory was issued for Fentora. Reports of serious adverse events, including deaths in patients taking Fentora had been reported to the Agency. The reports described prescribing to non-opioid tolerant patients, misunderstanding of dosing instructions, or inappropriate substitution of Fentora for Actiq by pharmacists and prescribers. Additionally, as a result of these reports, changes to the Package Insert and MedGuide were made in February 2008. These modifications, including changes to the Box Warning, strengthen the warnings regarding the use of Fentora in opioid non-tolerant patients including patients with migraines, correct dosing, and the conversion of patients from Actiq to Fentora.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 1, 2008
To:	Bob Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Rheumatology Products Office of New Drugs Center for Drug Evaluation and Research
Thru:	Solomon Iyasu, M.D., M.P.H. Director Division of Epidemiology Office of Surveillance and Epidemiology Center for Drug Evaluation and Research
From:	LCDR Kendra Worthy, Pharm.D. Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology Center for Drug Evaluation and Research Laura Governale, Pharm.D., MBA Drug Use Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology Center for Drug Evaluation and Research
Subject:	Concurrency Analysis VOCON: Fentora® or Actiq® with pain market products
Drug Name(s):	Actiq®, Fentora®
Application Type/Number:	NDA 20-747, NDA 21-947
Applicant/sponsor:	Cephalon®
OSE RCM #:	2007-223

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CONTENTS

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Rheumatology Products is holding an Advisory Committee meeting on May 6, 2008, in which an expanded indication for Fentora®, NDA 21-947, for non-cancer related pain will be discussed.

This review describes the estimated proportion of patients who are on concurrent therapy with Actiq® or Fentora® with products in the pain market. We examined the annual number of patients who filled a prescription for Actiq® or Fentora® in the outpatient retail pharmacy setting and who also received concurrent prescription products within the pain market. Analyses included three calendar years from 2005 through 2007 for Actiq®, and year 2007 for Fentora®. The Verispan, Vector One®: Concurrency (VOCON) tool was used to conduct this analysis. Data from VOCON are unprojected patient counts and may not be generalized to all U.S. patients.

- In year 2005, approximately **40%** of patients who filled a prescription for **Actiq®** were on concurrent therapy with a product from the pain market, where the product from the pain market was filled first.
- In year 2007, approximately **26%** of patients who filled a prescription for **Actiq®** were on concurrent therapy with a product from the pain market, where the product from the pain market was filled first.
- In year **2007**, approximately **59%** of patients who filled a prescription for **Fentora®** were on concurrent therapy with a product from the pain market, where the product from the pain market was filled first.
- The majority of diagnoses associated with Actiq® and Fentora® during year 2007 were non-cancer related.
- Anesthesiology (17%), Physical Medicine and Rehabilitation (16%), and Family Medicine (12%) were the leading prescribing specialties for Actiq® during year 2007.
- Physical Medicine and Rehabilitation (21%), Anesthesiology (18%), and Anesthesiology, other (16%) were the leading prescribing specialties for Fentora® during year 2007.

The analysis found a higher prevalence of concurrent therapy with products in the pain market for Fentora® than Actiq®. The data also suggests that off-label prescribing is not uncommon with Fentora® and Actiq®

1 BACKGROUND

1.1 INTRODUCTION

Actiq® was approved on November 4th, 1998, under NDA 20-747 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. Fentora® was approved on September 25, 2006, under NDA 21-947 for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Both Actiq® and Fentora® have risk management plans in place that include minimizing use by opioid non-tolerant individuals. Results of this concurrency analysis may be presented at the Division of Anesthesia, Analgesia, and Rheumatology Products Advisory Committee scheduled for May 6, 2008, in which an expanded indication for Fentora® for non-cancer related pain will be discussed.

2 METHODS AND MATERIALS

Using the currently available data resources, this review describes the estimated proportion of patients who are on concurrent therapy with Actiq® or Fentora® with the pain market, and thus potentially gauge use among non-opioid tolerant patients. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

2.1 PRODUCTS AND DATA SOURCES

Utilizing the Verispan Vector One®: Concurrency (VOCON) tool, we queried for concurrent use of Actiq® or Fentora® with products within the pain market. The USC classes and products that comprise the pain market are listed in Appendix 2, Table 1. Twelve sets of reports were generated from concurrency scenarios that were set up using a 10% grace period of overlapping days supply concurrency method. Analyses included three calendar years from 2005 through 2007 for Actiq®, and year 2007 for Fentora®. Data were analyzed for concurrency with Actiq® or Fentora® and the entire pain market defined by Verispan, stratified by USC Class and product.

An episode of concurrency is identified when a prescription in the Base group (Actiq® or Fentora®) overlaps with the days supply for a dispensed prescription in the Concurrent group (pain market or USC/product within the pain market). The days supply is calculated by adding the number of *therapy days* to the time of prescription dispensing. The number of *therapy days* is estimated by dividing the number of tablets or units dispensed by the number of tablets or units consumed per day. A grace period of 10% is allowed for the days supply time window to adjust for delays in prescription filling. For each report, the fill sequence was defined as Concurrent group (Pain market, or USC or product within pain market filled before Base group (Actiq® or Fentora®).

Outpatient use stratified by physician specialty was measured using Verispan, LLC: Vector One®: National (VONA). Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (PDDA) database. Complete descriptions of the databases used can be found Appendix 1.

3 RESULTS

3.1 PAIN MARKET CONCURRENCY

Table 2 (see Appendix 2) shows the number (and percentage) of patients on concurrent therapy with Actiq® and the entire pain market from year 2005 through 2007.

- The number of patients that filled a prescription for Actiq® in retail pharmacies decreased from 27,031 patients in year 2005 to 24,141 in year 2006, down to 6,724 patients in year 2007.

- Overall, the number of patients on concurrent therapy with a product from the pain market and Actiq® has decreased from approximately 10,869 patients (40%) in year 2005 to 1,755 patients (26%) in year 2007.

- The average number of concurrent days in year 2005 was 41 days, which represented approximately 17% of the total days supply for Actiq® prescriptions. In year 2007, the average number of concurrent days was 35 days, representing 11% of the total days supply for Actiq® prescriptions.

Table 3 (*see Appendix 2*) shows the the number (and percentage) of patients on concurrent therapy with Fentora® and the entire pain market for year 2007.

- In year 2007, approximately 5,636 patients (59%) filled a prescription for a medication from the pain market then concurrently filled a prescription for Fentora®.
- The average number of concurrent days was 53 days, which represented approximately 42% of the total days supply for Fentora® prescriptions.

3.2 Concurrency by Class

Table 4 (see Appendix 2) shows the number (and percentage) of patients on concurrent therapy with Actiq® and the pain market stratified by USC Class during years 2005 through 2007.

- During years 2005 and 2006, patients identified as having filled a prescription for Actiq® were more frequently on concurrent therapy with a product from USC Class 02232 "Codeine and Combination, Non-Injectable". Approximately 6,019 patients (22%) and 5,120 patients (21%), during years 2005 and 2006, respectively, had already filled a prescription for a product from this class prior to receiving a prescription for Actiq®.
- In year 2007, patients identified as having filled a prescription for Actiq® were more frequently on concurrent therapy with a product from USC Class 02222 "Morphine and Opium, Non-Injectable". Approximately 1,071 patients (16%) had already filled a prescription for a product from this class prior to receiving a prescription for Actiq®.

Table 5 shows the number (and percentage) of patients on concurrent therapy with Fentora® and the pain market stratified by USC Class during year 2007.

- Patients identified as having filled a prescription for Fentora® in year 2007 were more frequently on concurrent therapy with a product from USC Class 02222 "Morphine and Opium, Non-Injectable". Approximately 3,676 patients (39%) had already filled a prescription for a product from this class prior to receiving a prescription for Fentora®.
- USC Class "Codeine and Combination, Non-Injectable" was the second most frequent class of products that patients were on concurrent therapy with Fentora®. Approximately 3,211 patients (34%) were on a product from this class prior to receiving a prescription for Fentora®.

3.3 Concurrency by Product

Table 6 shows the number (and percentage) of patients on concurrent therapy with Actiq® and the pain market stratified by top ten products during years 2005 through 2007.

- Overall, from years 2005-2007, patients identified as having filled a prescription for Actiq® were more frequently on concurrent therapy with a hydrocodone/apap product. Approximately 2,672 patients (10%) in year 2005, 2,257 patients (9%) in year 2006, and 407 patients (6%) in year 2007 were on prior therapy with a hydrocodone/apap product before filling a prescription for Actiq®.

- Fentanyl transdermal was the second most frequent product in the pain market that Actiq® patients were on concurrent therapy with. Approximately 1,613 patients (6%) in year 2005, 1,796 (7%) in year 2006, and 407 patients (6%) in year 2007 were on prior therapy with a fentanyl transdermal product before filling a prescription for Actiq®.

- Oxycodone (immediate release) was the third most frequent product in the pain market product that Actiq® patients were on concurrent therapy with. Approximately 1,238 patients (5%) in year 2005, 1,285 patients (5%) in year 2006, and 243 patients (4%) in year 2007 were on prior therapy with an immediate release oxycodone product prior to filling a prescription for Actiq®.

Table 7 shows the number (and percentage) of patients on concurrent therapy with Fentora® and the pain market stratified by top ten products during year 2007.

- Patients identified as having filled a prescription for Fentora® in year 2007 were more frequently on concurrent therapy with a fentanyl transdermal product. Approximately 1,400 patients (15%) were on prior therapy with a fentanyl transdermal product before filling a prescription for Fentora®.

- Hydrocodone/APAP was the second most frequent product in the pain market product that Fentora® patients were on concurrent therapy with. Approximately 1,296 patients (14%) in year 2007 were on prior therapy with a hydrocodone/apap product before filling a prescription for Fentora®.

- Oxycodone (immediate release) was the third most frequent product in the pain market product that Fentora® patients were on concurrent therapy with. Approximately 1,029 patients (11%) in year 2007 were on prior therapy with an immediate release oxycodone product before filling a prescription for Fentora®.

Table 8 (*see Appendix 2*) shows the overall concurrency between Actiq® and hydrocodone/apap products from year 2005 through 2007.

- Overall, the number of Actiq® patients on concurrent therapy with hydrocodone/apap products has decreased from approximately 2,672 patients (10%) in year 2005 to 407 (6%) patients in year 2007.

- The average number of concurrent days between Actiq® and hydrocodone/apap products in year 2005 was 23 days, which represented approximately 2% of the total days supply for Actiq® prescriptions. In year 2007, the average number of concurrent days was 21 days, representing 2% of the total days supply for Actiq® prescriptions.

Table 9 (*see Appendix 2*) shows the overall concurrency between Fentora® and fentanyl transdermal products for year 2007.

- In year 2007, approximately 15% of patients who filled a prescription for Fentora® were on concurrent therapy with a fentanyl transdermal product.

- There was an average 46 concurrent days between Fentora® and fentanyl transdermal products which represented approximately 9% of the total days supply for Fentora® prescriptions.

Table 10 (see Appendix 2) shows the projected uses, stratified by diagnosis, of Actiq® and Fentora® during patient visits in office-based physician practices.

- The majority of diagnoses associated with Actiq® or Fentora® during year 2007 were non-cancer related.

Table 11 (see Appendix 2) shows the projected number of prescriptions, by physician specialty, for Fentora® and Actiq® dispensed from U.S. Retail Pharmacies during year 2007.

- Anesthesiology (17%), Physical Medicine and Rehabilitation (16%), and Family Medicine (12%) were the leading prescribing specialties for Actiq® during year 2007.

- Physical Medicine and Rehabilitation (21%), Anesthesiology (18%), and Anesthesiology, other (16%) were the leading prescribing specialties for Fentora® during year 2007.

4 DISCUSSION

The findings from this consult should be interpreted in the context of the known limitations of the databases used. When examining fill sequence, several assumptions are made: (1) that a patient is taking the prescription(s) as recommended; and (2) the days supply for a prescription is recorded to reflect how the patient is actually taking the prescription.

In this analysis, we queried for concurrent use of a product within the pain market, specifically an opioid, with Actiq® or Fentora®, and used this as a surrogate for examining opioid tolerance. Oral transmucosal fentanyl citrate, the generic formulation of Actiq®, was not included in the base group along with Actiq® in this analysis. During the most recent calendar year 2007, approximately 26% of patients receiving a prescription for Actiq® were on concurrent therapy with a product within the pain market, as compared to 40% during year 2005. The decrease in the proportion of concurrency between Actiq® and the pain market over the years may be due to the increased off-label use of this product in non-opioid tolerant populations. Examination of concurrent usage of the generic oral transmucosal fentanyl citrate product with the pain market will be undertaken in a later analysis for comparative purposes.

Although nearly 60% of Fentora® patients are on concurrent therapy with a product in the pain market, the majority of this product is used off-label in the non-cancer population (see Table 10, Appendix 2). Furthermore, this product is most commonly prescribed by Physical Medicine and Rehabilitation specialists in the outpatient setting which further reflects off-label use (see Table 11, Appendix 2).

Verispan's Vector One®: Concurrency does not capture data from inpatient hospitals, oncology clinics, same-day surgery centers, or mail order pharmacies. Although nearly 87% of Fentora® and 84% of Actiq® products were distributed to outpatient retail pharmacy settings during year 2007, true opioid tolerance/non-tolerance cannot be determined within the confines of this analysis, as a patient could begin opioid treatment as an inpatient or in a clinic, and continue therapy as an outpatient[1] (data not shown). Further epidemiological analysis would be required to

[1] IMS HEALTH, IMS National Sales PerspectiveTM, Jan.-Dec. 2007, data extracted 3-2008. Source File: NSPC 2008-226 Fentora Actiq sales 3-28-08 0803acfe.xls

study patients' courses of therapy across these settings. The data presented in this review are all based on analysis of **unprojected patient** counts and they cannot be generalizated to the national level.

5 CONCLUSIONS

From years 2005-2007, the number of patients that filled a prescription for Actiq® has decreased as well as the percentage of patients on concurrent therapy with Actiq® and a product from the pain market. In year 2005, approximately 40% of patients who filled a prescription for Actiq® also filled a prescription from the pain market. This proportion decreased to approximately 26% in year 2007. In year 2007, approximately 59% of patients that filled a prescription for Fentora® also filled a prescription from the pain market. Hydrocodone/APAP, fentanyl transdermal, and oxycodone (immediate release) products were the most common concurrent products within the pain market. The majority of use for Actiq® and Fentora® is occurring in the outpatient setting for non-cancer indications. Anesthesiology and Physical Medicine and Rehabilitation were the leading specialties that prescribed Actiq® and Fentora® prescriptions that were filled in retail settings. Concurrency analysis suggests that there is a higher prevalence for prescribing a medication from the pain market concurrently with Fentora® than with Actiq®. The data also suggest that off-label prescribing for non-cancer related conditions is not uncommon with Fentora® and Actiq®

CONCURRENCE

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APPENDICES

APPENDIX 1: DATABASE DESCRIPTION

Verispan, LLC: Vector One®: Verispan Concurrency (VOCON)

Data used in VOCON is derived from Verispan's Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims annually, representing over 160 million unique patients. Vector One® receives approximately half the of retail prescriptions dispensed nationwide. Verispan obtains all prescriptions from approximately one-third of the reporting stores and a significant sample of prescriptions from the remaining stores.

VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using four scenarios. These scenarios are (in order of most to least restrictive): Same day fills, overlapping days supply, overlapping days supply with % grace period, fills during the same time period.

The VOCON module provides unprojected patients counts. Nationwide projections are not available.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and

trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

APPENDIX 2: TABLES

Table 1: USC Classes included in the Pain Market*

Verispan, Vector One®: Concurrency Tool (VOCON). *Generic Products are included in this analysis but all generic products are not listed.

USC 02111 Ergot Derivatives, Alone/Combination

Cafergot	DHE-45
Ergomar	Ergocaff-PB
Bellergal S	Sansert

USC 02112 Serotonin 5HT-1 Receptor Agonists

Imitrex Oral	Relpax
Maxalt (MLT)	Zomig (ZMT, NS)
Axert	Imitrex Statdoes Ref
Imitrex Nasal Spray	Frova
Amerge	Imitrex Staidose Pen
Imitrex Inj	

USC 02118 Anti-Migraine, Combination

Midrin	Duradrin
Migraten	Amidrine
Migrin-A	Migralam

USC 02120 Acetaminophen

USC 02131 Synthetic Non-Narcotic Injectable

Talwin Inj	Prialt
Nubain	Toradol IM
Stadol	

USC 02132 Synthetic Non-Narcotic Non-Injectable

Ultram (ER)	Advil (Children's)
Ultracet	Motrin (IB, Children's)
Ponstel	Equagesic
Anaprox (DS)	Talacen
Cataflam	Toradol Oral
Dolobid	Stadol NS

USC 02140 Salicylates and Related

Aspir-Low	Lanorinal
Fiorinal	Ecotrin (Max Str)
MST 600	Bayer Aspirin
Bayer Child Aspirin	Ascriptin (Max Str, A/D)
Bater Enteric	Easprin
Tetra-Mag	Salflex
Norwich Aspirin	Amigesic
Anacin (Max Str)	Bayer Aspirin Max
Bufferin Analgesic	Hyalex
Disalcid	Salsalate

USC 02150 Synthetic Non-Narcotic Combination

Dolgic Plus	Be-Flex-Plus
Durabac	Dolgic LQ
Levacet	Rhinoflex
Acuflex	Combiflex (ES)
Be-Flex-Plus	By-Ache
Vanquish	Alpain
Butalbital/ASA/Caffeine	

USC 02212 Propoxyphenes

Propoxyphene(/APAP, Cpd)	
Darvocet (N-100, A500, N-50)	Wygesic
Darvon (N, Compound-65)	Trycet

USC 02214 Synthetic Narcotic Non-Injectable

Meperitab	Methadone Non-inj
Demerol Non-Inj	Meperidine/Prometh.
Talwin-NX	Methadose
Dolophine HC Non-Inj	Meperidine Non-inj
Mepergan Fortis	Pentazocine/Naloxone
Levo-Dromoran Non-Inj	

USC 02221 Morphine and Opium Injectable

Buprenex	Morphine Sulf Inj
Dilaudid Inj	HydromorphoneInj
Dilaudid HP	Buprenorphine
Duramorph PF	
Astramorph PF	

USC 02222 Morphine and Opium Non-Injectable

Suboxone	Actiq®
Morphine Sulfate (CR,ER)	Opium Tinture
Kadian	Roxanol (T, 100)
Duragesic	Oramorph SR
Avinza	Dilaudid
Opana (ER)	RMS
Subutex	MSIR
Dilaudid Non-Inj	Opana
Fentora®	MS Contin
Oral Transmucosal Fentanyl Citrate	
Fentanyl Transdermal	
Morphine Sulfate Non-Inj	
Hydromorphone	

USC 02232 Codeine and Combination Non-Injectable

Hydrocodone/APAP(ASA)	Oxycodone/APAP(ASA)
Endocet	Oxy-IR
Oxycontin	Magnacet
M-Oxy	Panlor Dc
Roxicet	Stagesic
Vicodin (ES, HP)	Synalogos DC
Lortab (2.5,5,7,10)	Lortab Elixir
Percocet (2.5,7,10)	Co-Gesic
Norco	Maxidone
Vicoprofin Non-Inj	Margesic H
Tylenol (#2,#3, #4)	Reprexain
Roxilox	Narvox
Xodol	Perloxx
Lorcet (10, Plus, HD)	Anexsia
Fiorinal w/Codeine	OxyFast
Zydone	Tylenol w/Codeine
Zerlor	Trezix
Captial w/Codeine	Percolone
Combunox	Endocodone
Endodan	Liquicet

USC 02211 Synthetic Narcotic Analgesic Injectable	Acetaminophen/Caffeine	Hydrocet
Demerol Inj	Tylox	Hy-Phen
Meperidine Inj	Acetaminophen/Codeine	Tramadol(/APAP)
Methadone Inj		

Table 2: Total Number of Patients on Concurrent Therapy for Actiq® and all products within the pain market during Years 2005-2007. Pain Market products filled before Actiq®.

Drug Group A: Actiq®			Drug Group B: Pain Market							
Year	Patients (Actiq®)	Avg Patient Days Supply (Actiq®)	Patients (Conc)	Avg Patient Days Supply (Conc)	Total Patients (in Base OR Conc Group)	Total Patients (in Base AND Conc Groups)	Concurrent Patients	% Concurrent Patients of Actiq®	Avg Concurrent Days	Concurrent Days Share of Actiq®
2005	27,031	97	27,280,632	50	27,280,632	27,031	10,869	40.21%	41	16.77%
2006	24,141	97	27,950,470	54	27,950,470	24,141	8,950	37.07%	40	15.28%
2007	6,724	84	27,965,157	59	27,965,157	6,724	1,755	26.10%	35	10.60%

Source: Verispan Vector One™: Concurrency (VOCON), Years 2005-2007, data extracted March 2008 File: VOCON 2008-226 Actiq® Market.xls

Table 3: Total Number of Patients on Concurrent Therapy for Fentora® and all products within the pain market during Year 2007. Pain Market products filled before Fentora®.

Drug Group A: Fentora®			Drug Group B: Pain Market							
Year	Patients (Fentora®)	Avg Patient Days Supply (Fentora®)	Patients (Conc)	Avg Patient Days Supply (Conc)	Total Patients (in Base OR Conc Group)	Total Patients (in Base AND Conc Groups)	Concurrent Patients	% Concurrent Patients of Fentora®	Avg Concurrent Days	Concurrent Days Share of Fentora®
2007	9,486	74	27,965,157	59	27,965,157	9,486	5,636	59.41%	53	42.33%

Source: Verispan Vector One™: Concurrency (VOCON), Year 2007, data extracted March 2008 File: VOCON 2008-226 Fentora® Concurrency.xls

Table 4: Total Number of Concurrent Patients, by Pain Market Class, on Concurrent Therapy with Actiq during Years 2005-2007.
Pain Market Class filled before Actiq

Year	USC 02232 Codeine & Comb Non-Inj	USC 02222 Morphine & Opium Non-Inj	USC 02214 Syn Narcotic Non-Inj	USC 02132 Syn Non-Narc Non-Inj	USC 02112 Serotonin 5HT-1 Rec Agon	USC 02212 Propoxyphenes	USC 02120 Acetaminophen	USC 02140 Salicylates & Related	USC 02221 Morphine & Opium Inj	USC 02111 Ergot Deriv. Alone/Comb	USC 02211 Syn Narcotic Analg Inj	USC 02118 Anti Migraine, Comb	USC 02131 Syn Non-Narc Inj	USC 02150 Syn Non-Narc Combo
2005	6019 *(22.8)*	5930 *(19.0)*	1015 *(3.8)*	681 *(2.5)*	469 *(1.7)*	324 *(1.2)*	204 *(0.8)*	112 *(0.4)*	19 *(0.0)*	56 *(0.2)*	22 *(0.1)*	40 *(0.1)*	27 *(0.1)*	9 *(0.0)*
2006	5120 *(21.2)*	4339 *(18.0)*	804 *(3.3)*	552 *(2.3)*	449 *(1.9)*	234 *(1.0)*	156 *(0.6)*	81 *(0.3)*	15 *(0.1)*	38 *(0.2)*	23 *(0.1)*	31 *(0.1)*	23 *(0.1)*	9 *(0.0)*
2007	942 *(14.0)*	1071 *(15.9)*	159 *(2.4)*	99 *(1.5)*	57 *(0.8)*	40 *(0.6)*	36 *(0.5)*	22 *(0.3)*	9 *(0.1)*	8 *(0.1)*	6 *(0.1)*	5 *(0.1)*	1 *(0.0)*	1 *(0.0)*

Source: Verispan Vector One™: Concurrency (VOCON), Years 2005-2007, data extracted March 2008 File name: VOCON 2008-226 Actiq 2007 USC.xls

Table 5: Total Number of Concurrent Patients, by Pain Market Class, on Concurrent Therapy with Fentora during Years 2005-2007.
Pain Market Class filled before Fentora

Year	USC 02222 Morphine & Opium Non-Inj	USC 02232 Codeine & Comb Non-Inj	USC 02214 Syn Narcotic Non-Inj	USC 02132 Syn Non-Narc Non-Inj	USC 02112 Serotonin 5HT-1 Rec Agon	USC 02212 Propoxyphenes	USC 02120 Acetaminophen	USC 02140 Salicylates & Related	USC 02131 Syn Non-Narc Inj	USC 02111 Ergot Deriv. Alone/Comb	USC 02118 Anti Migraine, Comb	USC 02150 Syn Non-Narc Combo	USC 02221 Morphine & Opium Inj	USC 02211 Syn Narcotic Analg Inj
2007	3,676 *(38.8)*	3,211 *(33.8)*	600 *(6.3)*	326 *(3.4)*	241 *(2.5)*	126 *(1.3)*	119 *(1.3)*	46 *(0.5)*	17 *(0.2)*	17 *(0.2)*	15 *(0.2)*	12 *(0.1)*	11 *(0.1)*	6 *(0.1)*

Source: Verispan Vector One™: Concurrency (VOCON), Year 2007, data extracted March 2008 File name: VOCON 2008-226 Fentora Concurrency.xls

Table 6: Total Number of Concurrent Patients, by Top Ten Opioid Products, on Concurrent Therapy with Actiq during Years 2005-2007. Opioid Products filled before Actiq

Year	Hydrocodone/ APAP	Fentanyl Transdermal*	Oxycodone	Oral Transmucosal Fentanyl Citrate	Oxycodone w/APAP	Methadone Non-Inj	Oxycontin*	Duragesic*	Hydromorphone	Morphine Sulfate ER*
2005	2,672 *(9.9)*	1,633 *(6.0)*	1,238 *(4.6)*	—	964 *(3.6)*	432 *(1.6)*	1,108 *(4.1)*	1,283 *(4.7)*	527 *(1.9)*	478 *(1.8)*
2006	2,257 *(9.3)*	1,796 *(7.4)*	1,285 *(5.3)*	12 *(0.0)*	831 *(3.4)*	398 *(1.6)*	381 *(1.6)*	535 *(2.2)*	504 *(2.1)*	391 *(1.6)*
2007	407 *(6.1)*	401 *(6.0)*	243 *(3.6)*	177 *(2.6)*	162 *(2.5)*	100 *(1.9)*	122 *(1.6)*	117 *(1.7)*	99 *(1.5)*	80 *(1.2)*

*Extended release product

Source: Verispan Vector One™: Concurrency (VOCON), Years 2005-2007, data extracted March 2008 File name: VOCON 2008-226 Actiq Concurrency.xls

Table 7: Total Number of Concurrent Patients, by Top 10 Products, on Concurrent Therapy with Fentora during year 2007. Opioid Products filled before Fentora

Year	Fentanyl Transdermal*	Hydrocodone/ APAP	Oxycodone	Oral Transmucosal Fentanyl	Oxycodone/ APAP	Methadone Non-Inj	Hydromorphone	Oxycontin*	Duragesic*	Oxycodone CR*
2007	1,400 *(14.8)*	1,296 *(13.7)*	1029 *(10.8)*	550 *(5.8)*	528 *(5.6)*	483 *(5.1)*	380 *(4.0)*	355 *(3.7)*	312 *(3.3)*	305 *(3.2)*

*Extended Release Product

Source: Verispan Vector One™: Concurrency (VOCON), Year 2007, data extracted March 2008 File name: VOCON 2008-226 Fentora Concurrency.xls

Table 8: Total Number of Patients on Concurrent Therapy for Actiq® and hydrocodone during Years 2005-2007. Hydrocodone/APAP filled before Actiq®.

Drug Group A: Actiq®			Drug Group B: Hydrocodone/APAP							
Year	Patients (Actiq®)	Avg Patient Days Supply (Actiq®)	Patients (Conc)	Avg Patient Days Supply (Conc)	Total Patients (in Base OR Conc Group)	Total Patients (in Base AND Conc Groups)	Concurrent Patients	% Concurrent Patients of Actiq®	Avg Concurrent Days	Concurrent Days Share of Actiq®
2005	27,051	97	14,183,495	30	14,197,942	12,584	2,672	9.88%	23	2.39%
2006	24,141	97	14,877,804	33	14,890,834	11,111	2,257	9.35%	23	2.19%
2007	6,734	84	15,087,418	36	15,091,259	2,892	407	6.04%	21	1.52%

Source: Verispan Vector One™: Concurrency (VOCON), Years 2005-2007, data extracted March 2008 File: VOCON 2008-226 Actiq® Market.xls

Table 9: Total Number of Patients on Concurrent Therapy for Fentora® and fentanyl transdermal patches during Year 2007. Fentanyl transdermal filled before Fentora®.

Drug Group A: Fentora®			Drug Group B: Fentanyl Transdermal							
Year	Patients (Fentora®)	Avg Patient Days Supply (Fentora®)	Patients (Conc)	Avg Patient Days Supply (Conc)	Total Patients (in Base OR Conc Group)	Total Patients (in Base AND Conc Groups)	Concurrent Patients	% Concurrent Patients of Fentora®	Avg Concurrent Days	Concurrent Days Share of Fentora®
2007	9,486	74	434,122	115	440,247	3,361	1,400	14.76%	46	9.13%

Source: Verispan Vector One™: Concurrency (VOCON), Year 2007, data extracted March 2008 File: VOCON 2008-226 Fentora® Concurrency.xls

Table 10: Diagnoses Associated with the Use of Actiq and Fentora Mentioned During Patient Visits in Office-Based Practices in the U.S., Years 2005-2007.

	1/2005-12/2007 Uses	*Share %*
TOTAL MARKET	176,618	*100.0%*
Actiq	102,722	*58.2%*
3384 CHRONIC PAIN SYNDROME	14,552	*14.2%*
3530 BRACHIAL PLEXUS LESIONS	12,809	*12.5%*
7159 OSTEOARTHROSIS NOS	11,282	*11.0%*
5951 CHR INTERSTIT CYSTITIS	8,318	*8.1%*
9988 SURGICAL COMPLICAT NEC	7,400	*7.2%*
7222 DISC DISPLACEMENT NOS	7,400	*7.2%*
3440 QUADRIPLEGIA UNSPEC	7,400	*7.2%*
7242 LUMBAGO	6,745	*6.6%*
8050 FX CERVICAL VERTEBRA-CL	6,554	*6.4%*
V670 SURGERY FOLLOW-UP	6,554	*6.4%*
7226 DISC DEGENERATION NOS	6,554	*6.4%*
7331 PATHOLOGICAL FRACTURE	5,789	*5.6%*
1629 MAL NEO BRONCH/LUNG NOS	1,363	*1.3%*
Fentora	73,896	*41.8%*
3530 BRACHIAL PLEXUS LESIONS	18,449	*25.0%*
3559 MONONEURITIS NOS	9,225	*12.5%*
9534 BRACHIAL PLEXUS INJURY	9,225	*12.5%*
V458 OTH POSTSURGICAL STATUS	7,400	*10.0%*
7331 PATHOLOGICAL FRACTURE	7,400	*10.0%*
7245 BACKACHE NOS	6,045	*8.2%*
2506 DIAB W NEUROLOGIC MANIF	5,384	*7.3%*
8950 AMPUTATION TOE	5,384	*7.3%*
3572 NEUROPATHY IN DIABETES	5,384	*7.3%*

Verispan, Physician Drug and Diagnosis Audit (PDDA). Data extracted 2-2008. Source File: VONA 2008-256 Actiq Fentora Dx4 2-19-08.xls

Table 11: Projected Number of Prescriptions Dispensed for Fentora and Actiq from U.S. Retail Pharmacies by Top 10 Physician Specialties During Year 2007

	2007 Retail TRx (N)	*Share %*
TOTAL MARKET	156,690	*100.0%*
Actiq	65,921	*42.1%*
ANESTHESIOLOGY	11,022	*16.7%*
PHYSICAL MEDICINE & REHAB	10,604	*16.1%*
FAMILY MEDICINE	7,724	*11.7%*
ANESTHESIOLOGY, OTHER	7,493	*11.4%*
INTERNAL MEDICINE	5,652	*8.6%*
NEUROLOGY	3,731	*5.7%*
UNSPECIFIED	3,611	*5.5%*
NURSE PRACTITIONER	3,212	*4.9%*
PHYSICIAN ASSISTANT	1,932	*2.9%*
PAIN MEDICINE	1,286	*2.0%*
All Others	9,654	*14.1%*
Fentora	90,769	*57.9%*
PHYSICAL MEDICINE & REHAB	18,790	*20.7%*
ANESTHESIOLOGY	16,601	*18.3%*
ANESTHESIOLOGY, OTHER	14,882	*16.4%*
FAMILY MEDICINE	7,494	*8.3%*
INTERNAL MEDICINE	4,577	*5.0%*
NEUROLOGY	4,491	*4.9%*
NURSE PRACTITIONER	4,150	*4.6%*
PHYSICIAN ASSISTANT	3,164	*3.5%*
PAIN MEDICINE	3,098	*3.4%*
UNSPECIFIED	2,821	*3.1%*
All Others	10,701	*11.1%*

Verispan Vector One™: National (VONA). Extracted 2/2008
Original File: VONA Actiq Fentora MD 2-19-08.qry

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laura Governale
4/1/2008 09:07:25 AM
DRUG SAFETY OFFICE REVIEWER
Signed for LCDR Kendra Worthy, Pharm.D., Drug Use Data Analyst

Solomon Iyasu
4/1/2008 11:15:13 AM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 4, 2008
To:	Bob Rappaport, M.D., Director Division of Analgesics, Anesthetics, and Rheumatology Products HFD-170
Thru:	Ann McMahon, M.D., M.S., Acting Director Lauren Lee, Pharm.D., Safety Evaluator Team Leader Division of Adverse Event Analysis II, HFD-430
From:	Yoo Jung Chang, Pharm.D., Safety Evaluator Division of Adverse Event Analysis II, HFD-430
Subject:	AERS review of serious adverse events associated with the use of Actiq that were reported to the FDA in 2007
Drug Name(s):	Actiq® (fentanyl citrate) oral transmucosal lozenge
Application Number:	020747
Sponsor:	Cephalon
OSE RCM #:	2008-226

CONTENTS

EXECUTIVE SUMMARY

The Division of Analgesics, Anesthetics, and Rheumatology products (DAARP) requested a review of post-marketing adverse events associated with two fentanyl products, Actiq (lozenge on a stick) and Fentora (buccal tablet). This request was made in preparation for the May 2008 Advisory Committee meeting to discuss expanding the indication of Fentora to include breakthrough pain in *non-cancer* patients. A review of Actiq reports was requested because it is the only other FDA approved oral transmucosal fentanyl product available on the market with an extensive off-label use. Both Actiq and Fentora are approved only for breakthrough cancer pain. This review contains an analysis of serious adverse events that were reported in association with Actiq only; Fentora case review is being conducted in a separate OSE review.

The AERS database was searched for U.S. reports of serious adverse events associated with Actiq that were reported between 01/01/2007 to 12/31/2007. This timeline was selected because (1) the review of all cases from approval to present was too large to complete in an individual review given the limited time and resources, (2) the selected year had the greatest number of reports, and (3) to align the cases with Fentora (FDA approved in 2006) so the most relevant cases are reviewed since the issues surrounding overdose/abuse and the management of those issues (i.e. risk minimization plans) have changed over the years.

A total of 61 unique spontaneous Actiq cases were retrieved from AERS, and a review of these cases did not reveal any notable unexpected safety concerns associated with Actiq. Unlabeled adverse events, including cardiac arrest, ventricular fibrillation, ventricular tachycardia, coma, lethargy, loss of consciousness, delusion, and irritability, were mostly involved with overdoses of Actiq. Overdoses represented the majority (52%) of serious adverse event cases. Among the overdose cases, 50% were intentional (ie. misuse and suicide), 25% were accidental exposures in young children, 19% involved accidental overdoses, and 6% were of unknown intent. Actiq is labeled for the potential for abuse (legal or illicit) and accidental pediatric exposure with caution to keep out of the reach of children. Among the cases that did not report an overdose, drug dependence and dental disorders (ie. dental carries and tooth fracture/loss) were the most commonly reported adverse events; both of which are labeled for Actiq.

Death was reported in 9 of 61 cases. The causes of death were reported as apnea (1), cardio-respiratory arrest (1), fentanyl toxicity (2), multiple drug overdose (2), and unknown (3). Seven of 9 cases involved an overdose of Actiq; overdose is labeled for Actiq. In the two non-overdose related deaths, there was insufficient clinical evidence to conclude that Actiq was directly or solely related to the reported events. The 1st case involved the death of one fetus in a woman who was pregnant with twins; the surviving twin was born healthy. This case was confounded by the concomitant use of other medications with FDA pregnancy category C and D; Actiq is labeled as pregnancy category C. The 2nd case involved an adult male of unknown age with a history of morbid obesity who underwent gastric bypass surgery and had postoperative complications that necessitated several months of hospitalization, during which time he was weaned off all pain medications, including Actiq. The patient was found dead within one week of discharge and the physician suspected that the patient began taking Actiq, and possibly other opioids again and subsequently experienced respiratory failure and death. In this case, it is possible that the patient was not opioid tolerant, which could have contributed to the outcome.

No labeling or regulatory recommendations are warranted at this time. The 61 cases that were reviewed did not reveal any notable unexpected safety concerns associated with Actiq. DAEA will continue routine monitoring of adverse events associated with the use of Actiq.

1 BACKGROUND

1.1 INTRODUCTION

The Division of Analgesics, Anesthetics, and Rheumatology products (DAARP) requested a review of post-marketing adverse events associated with two fentanyl products, Actiq (lozenge on a stick) and Fentora (buccal tablet) in preparation for the May 2008 Advisory Committee meeting to discuss expanding the indication of Fentora to include breakthrough pain in *non-cancer* patients; a review of Actiq reports was requested because it is the only other FDA approved oral transmucosal fentanyl product available on the market with an extensive off-label use. Both Actiq and Fentora are approved only for breakthrough cancer pain. This review contains an analysis of serious adverse events that were reported in association with Actiq only; Fentora case review is being conducted in a separate OSE review.

1.2 REGULATORY HISTORY

Actiq was initially approved in November 1998 for the indication of breakthrough cancer pain. Since approval, there have been several changes related to the manufacturing, formulation (sugar-free formulation), and labeling; the most recent change occurred in Feb 2007 and involved updating the indications and usage section of the label to include patients 16 years of age and older.

1.3 PRODUCT LABELING

The following box warning, warnings, precautions, and adverse reactions are in the Actiq "Highlights of Prescribing Information" section of the labeling, revised 2/2007:

Black box warning:

> WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION
>
> and POTENTIAL FOR ABUSE
>
> *See full prescribing information for complete boxed warning.*
>
> - Must not be used in opioid non-tolerant patients. (1)
> - Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)
> - Life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. (5.1)
> - Contraindicated in management of acute or postoperative pain. (4)
> - Contains medicine in an amount that can be fatal to a child. Keep out of reach of children and discard opened units properly. (5.2)
> - Use with strong and moderate CYP450 3A4 inhibitors may result in potentially fatal respiratory depression. (7)

Warnings and precautions:

- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.1, 5.3)
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("ACTIQ Welcome Kit") (5.2,17.4)
- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.5, 5.7)
- Titrate ACTIQ cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to hypoventilation. (5.5, 5.7)
- Administer ACTIQ with extreme caution in patients susceptible to intracranial effects of CO_2 retention. (5.6)

Adverse reactions:

- Most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. (6.1)
- Most common adverse reactions during treatment (frequency ≥5%); dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)
- Dental decay has been reported. (6.2)

2 MATERIALS AND METHODS

2.1 INTRODUCTION

The adverse event reporting system database (AERS) is a voluntary reporting system for health care professionals and consumers to report adverse events. Due to the voluntary system, there is underreporting and also duplicate reporting of adverse events. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues.

2.2 AERS CRUDE COUNTS

Search Criteria

The AERS database was searched for AERS crude count reports of all adverse events associated with Actiq from November 1998 to March 19, 2008, including U.S. and foreign reports.

2.3 AERS INDIVIDUAL CASE REVIEW

Search Criteria & Selection of Case Series

The AERS database was searched for U.S. reports of serious adverse events associated with Actiq, received by the Agency between 01/01/2007 – 12/31/2007. This time frame was selected for several reasons: (1) the burden of cases from approval to present was too large to complete an individual review given the limited time and resources (2) the selected year had the greatest

number of reports, and (3) to align the cases with Fentora (FDA approved 2006) so the most relevant cases are reviewed since the issues surrounding overdose/abuse and the management of those issues (i.e. risk minimization plans) have changed over the years. The cases were individually reviewed and duplicates were consolidated. The table below presents the number of cases retrieved from the AERS database and the number of cases that were included in the final review after exclusions:

Table 1. Selection of AERS Cases

Drug Name	Crude Counts	Cases Excluded (N=10)	Number of Cases Included
Actiq	74	• Adverse event is likely related to the underlying medical condition (1) • Adverse event is likely related to a concomitant medication (2) • Report requesting assistance with proper disposal of Actiq (7) • Duplicate reports (3)	61

3 RESULTS

3.1 AERS CRUDE COUNTS

For the AERS crude counts, individual reviews were not performed to determine an association between the reported events and the use of Actiq, primarily due to the large number of reports. Crude counts may include duplicates and the reported adverse events may not be directly related to Actiq use.

Table 2: Crude counts of AERS Reports for All Adverse Events associated with Actiq from FDA November 1998 to 3/19/2008 (US counts in parentheses)

	All reports (US)	Serious[1] (US)	Death (US)
Adults (≥ 17 yrs)	265 (236)	230 (202)	58 (47)
Pediatrics (0-16 yrs)	177 (176)	63 (62)	5 (5)
Age unknown (Null Values)	65 (55)	58 (48)	27 (20)
Total	507 (467)	351 (312)	90 (72)

[1] Serious adverse drug experience includes death, life threatening, hospitalization, disability, congenital anomaly, and other medically serious, per regulatory definition (CFR 314.80)

Figure 1: AERS reporting of crude counts for U.S and foreign Actiq reports from November 1998 to 3/19/2008

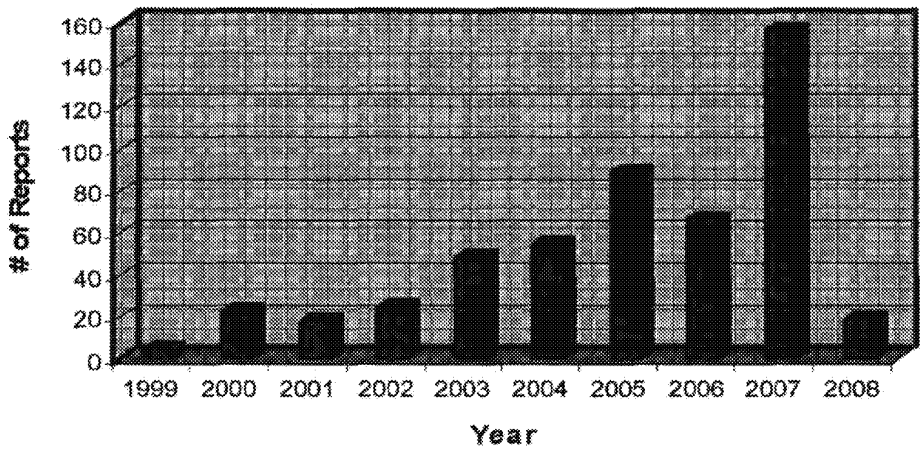

Table 3: Top 20 PTs from AERS crude counts of All Adverse Events (U.S. and foreign reports) associated with Actiq from November 1998 to 3/19/2008	
Accidental Drug Intake by Child (112)	Dental Caries (23)
Somnolence (69)	Medication Error (22)
Accidental Exposure (52)	Drug Abuser (21)
Lethargy (42)	Convulsion (20)
Vomiting (37)	Death (19)
Drug Dependence (32)	Pain (19)
Drug Withdrawal Syndrome (31)	Coma (18)
Nausea (30)	Pharmaceutical Product Complaint (18)
Overdose (27)	Respiratory Depression (15)
Drug Toxicity (26)	Tooth Loss (15)

3.2 AERS INDIVIDUAL CASE REVIEW

A total of 61 unique cases were retrieved from an AERS search for U.S. reports of serious adverse events associated with Actiq that were reported to the FDA in 2007. The reported adverse event terms from the cases were categorized according to the AERS system organ class (SOC) as shown below *(a report may contain more than one adverse event term)*:

Cardiac disorders [11]: tachycardia (4), cardiac arrest (3), cardiac failure congestive (1), pericarditis (1), ventricular fibrillation (1), ventricular tachycardia (1)

Eye disorders [3]: diplopia (1), mydriasis (1), pupil fixed (1)

Gastrointestinal disorders [46]: tooth loss (6), dental caries (5), tooth fracture (5), constipation (4), vomiting (3), nausea (2), dry mouth (2), tooth disorder (2), abdominal discomfort (1), abdominal distention (1), abdominal pain (1), abdominal pain upper (1), ageusia (1), diarrhoea (1), gastric hemorrhage (1), gastrointestinal motility disorder (1), gingival disorder (1), gingival pain (1), glossitis (1), intestinal obstruction (1), mastication disorder (1), oral pain (1), sensitivity of teeth (1), tongue discolouration (1), toothache (1)

General disorders and administration site conditions [18]: irritability (4), fatigue (2), accidental death (1), asthenia (1), chills (1), cold sweat (1), condition aggravated (1), drug effect decreased (1), drug interaction (1), gait disturbance (1), gingival discolouration (1), peripheral coldness (1), sudden death (1), swelling (1)

Hepatobiliary disorders [4]: alanine aminotransferase increased (2), aspartate aminotransferase increased (2)

Infections and infestations [4]: lung infection (1), pneumonia (1), pneumonitis (1), sinusitis (1)

Injury, poisoning and procedural complications [42]: accidental drug intake by child (8), drug toxicity (5), incorrect dose administered (4), overdose (4), inadequate analgesia (2), inappropriate schedule of drug administration (2), accident (1), application site ulcer (1), delirium tremens (1), device failure (1), drug administered at inappropriate site (1), drug administration error (1), drug exposure before pregnancy (1), drug exposure during pregnancy (1), drug prescribing error (1), fall (1), incorrect drug administration rate (1), injury (1), multiple drug overdose accidental (1), post procedural complication (1), post procedural hemorrhage (1), vascular access complication (1), wrong technique in drug usage process (1)

Investigations [9]: oxygen saturation decreased (2), weight decreased (2), blood creatine phosphokinase increased (1), blood glucose increased (1), pulse absent (1), toxicologic test abnormal (1), x-ray abnormal (1)

Metabolism and nutrition disorders [11]: acidosis (3), electrolyte imbalance (2), anion gap increased (1), anorexia (1), dehydration (1), hypokalemia (1), metabolic disorder (1), underweight (1)

Musculoskeletal and connective tissue disorders [5]: bone pain (1), muscle spasms (1), muscle rigidity (1), osteomyelitis (1), rhabdomyolysis (1)

Nervous system disorders [71]: somnolence (15), lethargy (13), coma (7), convulsion (5), dizziness (3), pain (3), loss of consciousness (3), headache (3), confusional state (2), tremor (2), vertigo (2), abnormal dreams (1), amnesia (1), ataxia (1), coordination abnormal (1), drug withdrawal convulsions (1), dysarthria (1), gait disturbance (1), grand mal convulsion (1), insomnia (1), hypoaesthesia (1), nystagmus (1), speech disorder (1), syncope (1)

Pregnancy, puerperium and perinatal conditions [3]: drug exposure during pregnancy (1), intra-uterine death (1), twin pregnancy (1)

Psychiatric disorders [52]: drug withdrawal syndrome (10), drug dependence (6), suicide attempt (6), agitation (5), hallucination (4), delusion (4), intentional drug misuse (4), anxiety (2), paranoia (2),completed suicide (1), delirium (1), depression (1), major depression (1), mental disorder (1), suicidal ideation (1), thinking abnormal (1), withdrawal syndrome (1), abnormal behaviour (1)

Renal and urinary disorders [1]: nephrolithiasis (1)

Respiratory, thoracic and mediastinal disorders [17]: respiratory depression (3), respiratory arrest (3), cyanosis (2), respiratory failure (2), respiratory depression (2), dyspnoea (1), pulmonary malformation (1), respiratory disorder (1), respiratory rate decreased (1), apnoea (1)

Social circumstances [14]: drug abuser (6), treatment noncompliance (2), impaired work ability (2), economic problem (1), impaired driving ability (1), pharmaceutical product complaint (1), bedridden (1)

Surgical and medical procedures [3]: drug detoxification (2), detoxification (1)

Vascular disorders [14]: hypertension (4), hypotension (2), deep vein thrombosis (2), haemodynamic instability (1), infarction (1), lymphoedema (1), pulmonary embolism (1), thrombosis (1), blood pressure abnormal (1)

A chart summary of the demographics and characteristics of the 61 cases is provided in the table below.

Table 4. Summary of demographics and characteristics of AERS serious adverse event reports associated with the use of Actiq in the U.S., reported in 2007 (N=61)		
Gender (N=60)		
	Male – 31	Female – 29
Age (N=53)		
	≤ 5 years	9
	16 – 19 years	6
	20 – 29 years	2
	30 – 39 years	11
	40 – 49 years	15
	50 – 59 years	8
	≥ 60 years	2
	Median = 39 years	
	Range = 1 day – 74 years	
Indication (N=57)		
	Cancer pain	3
	Non-cancer pain	31
	Intentional misuse / Suicide	15
	Accidental ingestion by a child	8
Specific Indication for Non-cancer Pain[¥] (N=31)		
	Abdominal pain – 2	Migraine – 3
	Back pain – 13	Neck pain – 3
	Conscious sedation – 1	Nerve pain – 3
	Fibromyalgia – 1	Pain, unspecified – 4
	Leg pain – 4	Shoulder/Arm/Hand pain – 4
	Lymphoedema – 1	

Table 4. Summary of demographics and characteristics of AERS serious adverse event reports associated with the use of Actiq in the U.S., reported in 2007 (N=61)		
Daily Dose[4] (N=22)		
	≤ 1200 mcg	3
	1300 – 2400 mcg	6
	2500 – 3600 mcg	1
	3700 – 4800 mcg	5
	4900 – 7200 mcg	4
	7300 – 9600 mcg	2
	15600 mcg	1
	Median = 3900 mcg	
	Range = 400 – 15600 mcg	
Opioid Tolerance[5] (N=20)		
	Tolerant – 16	Non-tolerant – 4
Concomitant Opioid Medications[6] (N=28)		
	Fentanyl Patch – 12	Oxycodone – 5
	Hydrocodone/Acetaminophen – 4	Oxycodone/Acetaminophen – 5
	Hydromorphone – 5	Propoxyphene/Acetaminophen – 1
	Methadone – 3	Sufentanyl – 1
	Morphine – 5	Tylenol with codeine – 1
Outcome[8] (N=61)		
	Death – 9	Life Threatening – 6
	Disability – 2	Medically Significant – 25
	Hospitalization – 28	
Event Year (N = 50)		
	2000 – 2003	4
	2004	4
	2005	13
	2006	19
	2007	10
Reporter Type		
	Healthcare Professional – 15	American Association of Poison Control Ctr – 23
	Consumer – 18	Attorney (class action lawsuit) – 5
Type of Report		
	15-Day	59

Table 4. Summary of demographics and characteristics of AERS serious adverse event reports associated with the use of Actiq in the U.S., reported in 2007 (N=61)		
	Direct	1
	Periodic	1

[a] These specific indications were obtained from the 31 cases that reported the use of Actiq for management of non-cancer pain. Cases may have reported more than one indication of pain.

[b] The daily dose was extrapolated based on the reported dose. In instances where a range was reported, an average of the lowest and highest dose was used to extrapolate a daily dose.

[c] Opiod tolerance was assessed based on the concomitant medications reported and per the labeling for Actiq: Patients were considered opioid tolerant if they reported taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer. Accidental ingestions by young children were assumed to be non-tolerant patients, but were excluded from the count.

[d] Cases may have reported more than one concomitant opioid medication.

[e] Cases may have reported more than one outcome.

4 DISCUSSION (FOR INDIVIDUAL CASE REVIEW)

Males (51%) and females (48%) were fairly equally represented. The age range was one day to 74 years, with a median of 39 years. Nine cases involved a pediatric patient, all ≤5 years of age. The majority of the cases reported *non-cancer* pain (51%) as the indication for use, and only a small percentage reported *cancer* pain (5%) as the indication. The remaining indications were intentional misuse, suicide and attempted suicide which accounted for 25% of the cases, and accidental exposure which accounted for 13% of the cases. Among the cases that reported using Actiq for the management of non-cancer pain, the majority reported back pain as the specific indication; others included shoulder/arm/hand pain, unspecified pain, leg pain, migraine, neck pain, nerve pain, and miscellaneous. The time to onset was not well documented. Only one case reported the time to onset of 90 minutes. The time to onset of specific events, such as dental caries, was calculated based on the therapy dates reported in the narrative.

Doses were not well documented in the reports. The daily dose was calculated for approximately one-third of the cases based on the reported dose and schedule. The daily dose of Actiq ranged from 400 – 19,600 mcg, with a median of 3,900 mcg. The cases were reviewed to determine whether the patient was opioid tolerant at the time of Actiq initiation. Based on the concomitant medications and therapy dates, 16 cases were opioid *tolerant* and 4 cases were *non-tolerant*; it was not possible to determine the tolerance in the remaining cases due to the limited information reported. The criteria used to consider whether a patient was opioid tolerant was as follows: "Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer."[1] Twenty-eight cases (46%) reported the concomitant use of another opioid, the most common was fentanyl patch. Twenty-three of 61 cases reported the concomitant use of other medications, excluding opioids.

The following outcomes were reported from this case series: death (9), disability (2), hospitalization (28), life-threatening (6), and medically significant (25). Cases may have reported more than one outcome.

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[1] Actiq labeling: Full Prescribing Information. Last revised 2/2007.

Although all 61 reports were received by the Agency in 2007, 50 reported an event date prior to 2007, and extending back to 2000. The year 2006 was the most frequently reported event year. A majority of the cases were submitted by the American Association of Poison Control Centers (38%), followed by consumers (30%), healthcare professionals (24%) and attorneys (8%). The majority of cases (97%) were submitted as expedited 15-day reports.

Notable adverse events are discussed below. Cases may be included in more than one section.

Deaths (N=9)

Nine cases reported a death outcome. The causes of death were reported as follows: apnea (1), cardio-respiratory arrest (1), fentanyl toxicity (2), multiple drug overdose (2), and unknown (3).

Seven of 9 cases involved an overdose: accidental exposure (1), suicide (1), intentional misuse (1), accidental overdose (3), and unknown intent (1). Three of the overdose cases reported a fentanyl blood level (2, 4, and 6 ng/mL)[2] and one case did not provide a value but reported that the fentanyl level was within the therapeutic range. Although the three cases that reported fentanyl levels were below or at the low end of the potentially fatal range, the cause of death was presumed to be related to Actiq because either the patient was opioid non-tolerant or no other cause of death was apparent. The **accidental exposure** case involved a one year old child who ingested an unknown amount of Actiq and reported cardiac arrest and death. The cause of death was reported as acute fentanyl intoxication (blood level of 6 ng/mL). The **suicide** case involved an intentional ingestion of an unknown amount of Actiq in a 53 year old woman, and reported cardiac arrest, ventricular fibrillation, ventricular tachycardia, seizures, coma and death. Recreational drug use was implicated in the **intentional misuse** case which involved a 17 year old male with a history of drug abuse who obtained Actiq and methadone illegally off the street and reported loss of consciousness and sudden death from an acute intoxication of combined fentanyl (blood level 2 ng/mL) and methadone. Three cases reported an **accidental overdose**. The 1st accidental overdose case involved a woman of unknown age who was taking Actiq 800 mcg (frequency and duration not reported) for back pain related to several back surgeries and died. Concomitant medications were reported as Dilaudid, fentanyl patch, and Valium. Blood levels of all her medications were reported to be within therapeutic range; therefore, the cause of death was reported as a multiple drug overdose. The 2nd case involved a 40 year old woman who was taking Actiq 1600 mcg three times daily for an unknown duration and died. According to the autopsy report and death certificate the patient died from apnea related to fentanyl toxicity (levels not reported); however, the patient's physician reported that her cause of death was likely due to her underlying medical condition (details were not reported) and the high levels of fentanyl referred to in the toxicology report were likely due to the patient's opioid tolerance and requirement for higher doses of fentanyl (dose not reported). The patient's medical history included immunoglobulin deficiency, rheumatoid arthritis, osteoarthritis, pulmonary fibrosis secondary to Vioxx, recurring electrolyte imbalances, thoracic outlet syndrome, intervertebral disc degeneration, and fibromyalgia. The 3rd case involved involved a 35 year old woman who was opioid non-tolerant and was initiated on Actiq 800 mcg (frequency and duration not reported) for an unspecified non-cancer pain and died. The autopsy report stated that although the blood level of fentanyl (3 ng/mL) was low, she was believed to be an opioid non-tolerant patient and no other cause of death was apparent; therefore, the conclusion was that the cause of death was due to fentanyl poisoning. The one case that reported an overdose of **unknown intent** involved a 55 year old man who reportedly overdosed on fentanyl (dose, frequency, duration, and indication were not reported) and died. The patient was taking Duragesic and Actiq. No other information was reported.

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[2] Fentanyl therapeutic drug concentration for analgesia is 0.2 to 1.2 ng/mL (www.csi.unionmedex.com- Prod Info Duragesic(R), 2001)

Among the two cases that did not report an overdose, the 1st case reported the death of a fetus in a woman who was pregnant with twins and had been taking Actiq (FDA pregnancy category C) prior to and during the pregnancy. She was on Actiq therapy for several years (dose not specified) for unspecified gastrointestinal issues and had taken Actiq before and during the entire pregnancy. The surviving twin was born healthy with the exception of requiring narcotic withdrawal treatment. Concomitant medications were Xanax (FDA pregnancy category D), Phenergan (FDA pregnancy category C), and Duragesic (FDA pregnancy category C). The 2nd case involved an adult male of unknown age with a history of morbid obesity who underwent gastric bypass surgery and had postoperative complications that necessitated several months of hospitalization, during which time he was weaned off all pain medications, including Actiq. The patient was found dead within one week of discharge and the physician suspected that the patient began taking Actiq, and possibly other opioids again and subsequently experienced respiratory failure and death.

It is likely that the two deaths from accidental exposure and suicide were associated with Actiq overdoses based on the descriptions surrounding the events. In the other 5 overdose cases it is possible that Actiq played a role in the deaths based on temporal association; however four of the cases were confounded by concomitant medications. Actiq is labeled for these events which include the potential for abuse (legal or illicit), risk of fatal overdose due to respiratory depression, contraindication in opioid non-tolerant patients, and accidental pediatric exposure with caution to keep out of the reach of children. In the two cases that did not report an overdose, the contributory role of Actiq could not be ruled out. The 1st case involving intra-uterine death was confounded by a twin pregnancy and concomitant medications, one of which was pregnancy category D. Actiq is labeled with pregnancy category C; there are no adequate and well-controlled studies in pregnant women. The 2nd case involving gastric bypass and death was based on the physician's assumption that the patient was no longer opioid tolerant and had ingested Actiq and possibly other opioids.

Cardiac disorders (N=9)

Nine cases reported the following cardiac related adverse events: *cardiac arrest (3), cardiac failure congestive (1), pericarditis (1), tachycardia (4), ventricular fibrillation (1), and ventricular tachycardia (1).*

Six of 9 cases involved an overdose: accidental exposure (2), suicide/suicide attempt (2), intentional misuse (1), and accidental overdose (1). Doses were not reported in any of the six overdose cases. The two **accidental exposure** cases involved children one year of age who accidentally ingested Actiq; the 1st case reported cardiac arrest (discussed in the death section) and the 2nd case reported tachycardia, coma, convulsion, hypertension, and muscle rigidity requiring hospitalization, intubation and treatment with various medications. The outcome was not reported in the 2nd case. Two cases reported a **suicidal attempt**; one of which was fatal. The suicide attempt case reported tachycardia and hypertension following the ingestion of Actiq; the patient was managed in a non-healthcare facility but the outcome was unknown. The completed suicide case reported cardiac arrest, ventricular tachycardia, ventricular fibrillation, coma, convulsion, and respiratory arrest and was treated in a critical care unit with CPR, cardioversion, intubation, and intravenous medications (discussed in the death section). One case involved an **intentional misuse** of Actiq chronically and reported tachycardia, hypertension, delusions, and hallucinations. This patient was treated at a healthcare facility with charcoal and the events were reported as resolved. The one **accidental overdose** case reported taking Actiq for more than three months and experienced tachycardia, delusions and hallucinations. The patient was treated in a critical care unit and received various medications; the outcome was not reported. No other information was provided. The remaining 3 of 9 cases did not report an overdose of Actiq. The 1st case involved a female of unknown age who reported **pericarditis** and rhabdomyolysis

following two years of Actiq therapy for back pain and renal calculi. The dose was 1200 mcg every four hours. Concomitant medications included Valium, Vicodin, and Duragesic. She had a past medical history of glomerulonephritis, chronic renal calculi, and addiction and abuse of opioids and other medications. No other details regarding the pericarditis and rhabdomyolysis were provided in the report, and her physician was not aware of these events. The 2nd case involved a 43 year old pregnant woman who was diagnosed with **congestive heart failure** a few days after delivery (discussed in the death section). She was on Actiq therapy for several years (dose not specified) for gastrointestinal issues and had taken Actiq throughout the pregnancy. The woman was pregnant with twins and reported intra-uterine death in one and the other was born healthy with the exception of requiring narcotic withdrawal treatment. She reported extreme swelling and high blood pressure several weeks before delivery. The day after she was discharged home from delivery, she experienced "lack of breath" and was hospitalized and diagnosed with congestive heart failure. It was reported that she had a very low ejection fraction, but no values were reported. At the time of the report (approximately 10 months following diagnosis), she continued to have congestive heart failure. Concomitant medications were Xanax, Phenergan, and Duragesic. The 3rd case involved a 50 year old man who was diagnosed with pulmonary embolism (PE), deep vein thrombosis (DVT), thrombosis, and respiratory failure leading to a **cardiac arrest**. This case is confounded by a past medical history significant for a total knee replacement and leg thrombosis. He had been taking Actiq for two years for chronic back and knee pain and was being weaned off at the time of the event; the dose was 200 mcg twice daily. Concomitant medications included immediate release morphine, MS Contin, and Celebrex.

The 6 cases of overdose that reported tachycardia (4), cardiac arrest (1), and ventricular fibrillation, ventricular tachycardia & cardiac arrest (1) were likely associated with an overdose of Actiq based on the temporal association and description surrounding the events. Actiq is not labeled for cardiac arrest, ventricular fibrillation or ventricular tachycardia; however, tachycardia has been reported in a long-term extension study in less than 1% of the patients. The role of Actiq in the non-overdose cases involving pericarditis and congestive heart failure could not be ruled out because of a positive temporal association. Additionally, these two cases were confounded by several concomitant medications; however, none were labeled for pericarditis, rhabdomyolysis, or congestive heart failure. Pericarditis and congestive heart failure are not labeled events for Actiq. The cardiac arrest case that did not involve an overdose was unlikely related to Actiq, and most likely related to pulmonary embolism and respiratory failure, but was included because this patient also reported respiratory depression, and Actiq's contributory role in the respiratory event could not be ruled out.

Gastrointestinal disorders (N=21)

Twenty-one cases reported adverse events related to gastrointestinal disorders. Notable adverse events are discussed below. Some cases may be included in more than one section.

Nine cases reported **gastrointestinal (GI) adverse events**; the 1st case reported intestinal obstruction in an adult female who was taking Actiq and Duragesic (doses unknown) for lymphoedema (probably to treat pain from lymphoedema, but the indication was reported as "lymphoedema"). This case was confounded by a past medical history of intestinal obstruction. No additional information was reported. The 2nd case reported gastric hemorrhage in a 50 year old man who also experienced a PE, DVT, respiratory failure and cardiac arrest (discussed in the cardiac section). He had been taking Actiq for two years for chronic back and knee pain and was being weaned off at the time of the event; Actiq dose was 200 mcg twice daily. Concomitant medications included immediate release morphine sulfate, MS Contin, and Celebrex. No further details surrounding the gastric hemorrhage were reported. The 3rd – 6th cases reported constipation, which is a common side effect of opioids. In addition to constipation, one of the

cases also reported abdominal discomfort and gastrointestinal motility disorder; however, this patient had been on Duragesic and Actiq therapy for several years. The 7th and 8th cases reported abdominal pain; one of which was associated with Actiq withdrawal, per the patient, while switching from Actiq 1200 mcg to Fentora 400 mcg, and the other occurred within 5 days of initiating intrathecal morphine and was thought to be caused by an overdose of opioids. The 9th case reported abdominal distension and cardiac arrest in an accidental exposure that resulted in death (discussed in the death and cardiac sections).

Thirteen cases reported **dental caries and/or tooth fracture and loss**. Eight cases reported tooth loss or fracture, 3 reported dental caries, and 2 reported both tooth fracture and dental caries. One case reported a past history of unspecified dental problems. The age ranged from 26 – 59 years with the median of 45 years (n=11). The adverse events were described as tooth sensitivity, dental cavities (as many as up to 40 were reported in one case), dental fillings falling out, tooth breakage, and tooth spontaneously falling out. Two cases reported the loss of all teeth. The time to onset of dental event was calculated in 3 cases as within one month, 2 months, and approximately one year. The frequency of administration was reported in 8 cases and ranged from 2 – 14 times daily, with a mean of 4.5 times daily. One case reported that the tooth loss pattern directly correlated to where the lozenge was routinely placed. Six cases reported the following interventions: orajel for mouth pain (1), fillings (1), root canals (2), tooth extractions (3), bone grafts (1), and oral surgery (1). One case reported that the dental issues resulted in a sinus and bone infection that required a hospitalization for antibiotic therapy (duration of hospital stay was not reported). One case reported broken teeth as a result of a fall; not directly related to Actiq.

It is possible that dental caries, tooth loss and tooth fractures are associated with Actiq based on the temporal association. Actiq is labeled for dental decay of varying severity including dental caries, tooth loss, and gum line erosion; and it is labeled as containing approximately 2 grams of sugar per unit. It is likely that constipation and abdominal discomfort are associated with Actiq based on the pharmacology of the drug, and is labeled as such. The intestinal obstruction and gastric hemorrhage cases were included in this case series despite a significant past medical history or lack of information surrounding the events because the contributory role of Actiq could not be ruled out based on the temporal association of Actiq and the event. Intestinal obstruction and gastrointestinal hemorrhage have been reported in a long-term extension study and is labeled as such in the adverse reactions section of the full prescribing information for Actiq.

Injury, poisoning and overdoses (N=32)

Thirty-two cases reported adverse event terms related to a drug injury, poisoning or overdose. The cases were analyzed for the manner of overdose and further grouped into the following categories: accidental exposure in a young child (8), accidental overdose (6), suicide/suicide attempt (8), intentional misuse (8), and unknown intent (2). The outcomes were reported as follows: death (7), hospitalization (9), and medically significant (16).

Eight cases involved an **accidental exposure** in a young child. Adverse events included cardiac arrest (1), coma (2), convulsion (1), coordination abnormal (1), cyanosis (1), dizziness (2), hypertension (1), hypotension (1), lethargy (4), loss of consciousness (1), muscle rigidity (1), mydriasis (1), nausea (1), pneumonitis (1), respiratory arrest (1), somnolence (4), tachycardia (1), vertigo (2), and vomiting (2). The age ranged from 1 – 5 years, with a median of 1 year (n=8). The amount ingested was unknown in all 8 cases, however the lozenge strength was reported in seven cases and ranged from 200 – 1200 mcg. One case reported cardiac arrest and death (discussed in the death section), two cases reported a life-threatening event requiring intubation and treatment with intravenous medications, two cases reported an admission into a non-critical

care unit and treatment with charcoal, and the remaining three cases reported treatment at a healthcare facility with either naloxone or charcoal.

Six cases reported an **accidental overdose**. Adverse events included abdominal pain (1), agitation (1), apnea (1), coma (1), dehydration (1), delirium (1), delusion (1), drug withdrawal convulsions (1), electrolyte imbalance (1), hallucination (1), headache (1), hemodynamic instability (1), hypokalemia (1), inadequate analgesia (1), metabolic disorder (1), pain (1), respiratory disorder (1), tachycardia (1), and tremor (1). The age ranged from 35 – 50 years, with a median of 44 years (n=4). In two cases the patients were determined to be opioid tolerant, one case was determined to be non-tolerant, and the tolerance was unknown in the remaining three cases. One case reported inadequate analgesia and involved a woman who had been taking Actiq 1200 mcg three times daily and Oxycontin for many years for chronic back pain who was switched to an intrathecal morphine pump because of ineffective pain relief; however, the patient continued to take Actiq and Oxycontin in addition to being on the morphine pump and experienced nausea, vomiting, abdominal pain and headaches. The patient was hospitalized and treated with medications and discharged in eight days. Of the remaining three cases, one involved the initiation of Actiq in an opioid non-tolerant patient and reported a death outcome (discussed in the death section), and the other two cases provided very limited information stating that there was an unintentional ingestion of an unknown amount of Actiq; also, these 2 cases did not report an indication for use. Three of six cases did not report a concomitant medication, one case reported the concomitant use of other opioids but the adverse event was attributed to fentanyl toxicity, and the remaining 2 cases reported an overdose of multiple drugs. Three cases reported a death outcome (discussed in the death section), two other cases reported a hospitalization, and the remaining case was managed in a non-healthcare facility (treatment and facility not specified).

Eight cases reported a **suicide attempt,** one of which reported a fatality. Adverse events included: acidosis (1), agitation (3), anion gap increased (1), AST/ALT increased (1), cardiac arrest (1), coma (2), confusional state (1), convulsion (1), delusion (1), electrolyte imbalance (1), fixed pupil (1), hallucination (1), hypertension (2), irritability (3), lethargy (4), respiratory arrest (2), respiratory depression (2), somnolence (4), syncope (1), tachycardia (1), ventricular fibrillation (1), and ventricular tachycardia (1). Three cases reported requiring intubation and intravenous medications; two of which also received CPR. Three other cases were also referred to a healthcare facility; the 1st reported treatment with naloxone, the 2nd reported no symptoms and was held only for observation, and the 3rd was lost to follow up. Of the remaining two cases, one reported management at a non-healthcare facility (treatment and facility not specified) and was lost to follow up, and the other reported minor effects of lethargy and drowsiness which resolved with no intervention.

Eight cases reported an **intentional misuse**. Adverse events included: acidosis (1), agitation (1), AST/ALT increased (1), blood creatinine phosphokinase increased (1), coma (2), convulsion (1), cyanosis (1), delusion (1), hallucination (1), hypotension (1), irritability (1), lethargy (3), loss of consciousness (2), oxygen saturation decreased (1), pulse absent (1), respiratory depression (3), somnolence (4), sudden death (1), and tachycardia (1). The mean age among the intentional misuse cases was 19 years (n=8), which is significantly less than the mean age (39 years) for all reports in this case series. Three cases did not report any concomitant medications, one case reported the concomitant use of Effexor XR, Lamictal, Neurontin, Klonopin, Trazodone and Estratest, and the remaining four cases also reported the misuse of concomitant medications/substances (ie. methadone-1 and an unspecified substance-3). One case reported a death outcome and the cause of death was reported as fentanyl and methadone toxicity (discussed in the death section). Among the remaining 7 cases, one reported requiring intubation and

intravenous medications, four reported naloxone or charcoal treatment, and the remaining 2 cases did not report any treatment.

In 2 of the cases, the overdose was of **unknown intent.** The adverse events reported in these cases included: delusion (1), hallucination (1), lethargy (1), and somnolence (1). One case reported a death outcome and the cause of death was reported as fentanyl toxicity (discussed in the death section). The outcome of the remaining case was unknown, but the events were considered to be due to fentanyl toxicity.

In summary, deaths and serious adverse events have been associated with overdoses of Actiq. Actiq is labeled for the potential for abuse (legal or illicit), risk of fatal overdose due to respiratory depression, and accidental pediatric exposure with a caution to keep out of the reach of children.

Nervous system disorders (N=34)

Thirty-four cases reported adverse events related to the nervous system. Notable adverse events are discussed below. Cases may be included in more than one section.

Six cases reported **convulsions**. All 6 cases were associated with either an Actiq overdose (2) or withdrawal (4). The time to onset was reported in only two cases as one day and one week. Two of 6 cases were confounded by both a history of seizure disorders and concomitant use of medications labeled for seizure or decreasing seizure threshold (ie. Adderall, Cymbalta, Geodon, and Depakote). In both cases, withdrawal of Actiq was reported as the cause of seizure. The 1st case involved a 46 year old man who had been taking Actiq for six years and had been seizure-free for the past four years while also on anticonvulsants. He also reported the concomitant use of Cymbalta, which is labeled for seizure. Twenty-four days after the patient stopped Actiq because of insurance reasons and started Dilaudid, he experienced a grand mal seizure requiring a hospitalization which he attributed to withdrawal symptoms; the outcome was not reported. The 2nd case involved a 30 year old man who reported taking fentanyl patch and Actiq and would run out of his supply by the end of the month and his physician would not prescribe additional doses resulting in withdrawal symptoms described as an inability to sit still, walking around in circles, and a sensation of crawling out of his skin. He also stated that on one occasion he was hospitalized for withdrawal symptoms and treated with Adderall, and experienced seizures. Concomitant medications labeled for seizure or decreasing seizure threshold included Adderall, Cymbalta, Geodon, and Depakote. Despite a history of seizures, this patient did not report the time of the last seizure and denied taking anticonvulsants, but reported taking Depakote for bipolar disorder. Two of six cases reported the concomitant use of sedative-hypnotics (ie. Ambien, clonazepam, and Valium); one of which was discussed above (2nd case involving the 30 year old) and the other involved a 3rd case of Actiq withdrawal. Therapy start and stop dates were not reported for the sedative-hypnotics in both cases. The 3rd case of Actiq withdrawal reported the concomitant use of a sedative-hypnotic and involved a 43 year old man who was taking Actiq 1200 mcg six times daily for shoulder pain for several years and abruptly discontinued Actiq due to cost. This case also involved a switch in therapy from Actiq 1200 mcg to Fentora 400 mcg, which is the recommended dose conversion[3]; then back to Actiq again. It was reported that he experienced seizures due to withdrawal and has since recovered from the event. Although seizures are not characteristic of adult opioid withdrawal syndrome, many methadone maintenance patients concomitantly abuse sedative-hypnotics which may result in seizures.[4] The

[3] Fentora labeling: Full Prescribing Information. Last revised Dec 5, 2007.

[4] Fine JS: Reproductive and perinatal principles. In: Goldfrank LR, Flomenbaum NE, Levin NA et al (Eds): Goldfrank's Toxicologic Emergencies, 6th ed, Appleton & Lange, Stamford, CT, 1998.

4th case of seizure associated with withdrawal involved a woman who had been taking Actiq for several years and acutely overdosed on Actiq, morphine and Oxycontin requiring a hospitalization, during which she experienced withdrawal symptoms including seizures. The remaining two cases that reported seizures involved Actiq overdoses: an accidental exposure in a one year old child and an intentional misuse in a 19 year old. In both cases, the patients experienced seizure, acidosis, and coma, and were hospitalized requiring intubation and various intravenous medications but the outcome was not reported in either case. Overall, no deaths were reported in any of the six cases. Four cases reported a hospitalization due to convulsions; one of which reported the events as resolved. The outcomes of the other cases were not known.

Twenty-six cases reported a **depressed level of consciousness**. The adverse event terms were coded as: *coma (7), confusional state (2), lethargy (13), loss of consciousness (3), somnolence (15), and syncope (1)*. Twenty-two of 26 cases involved an overdose; 2 of which were confounded by the use of other concomitant medications known to cause somnolence and lethargy (ie. methadone, Effexor, Lamictal, Neurontin, and Klonopin). Only one of twenty-two overdose cases reported a dose (400 – 800 mcg daily as needed), and the daily dose at which somnolence and loss of consciousness occurred was reported as 1200 mcg. The remaining 4 of 26 cases did not involve an overdose and reported the following adverse event terms: *confusional state (1), lethargy (1), and somnolence (2)*. The daily dose for these 4 cases ranged from 1600 – 16,800 mcg with a median of 5200 mcg (n=4). One case was considered to be opioid tolerant, one was non-tolerant, and the tolerance was unknown in the remaining 2 cases. All 4 cases reported the concomitant use of other opioids (ie. Darvocet, hydrocodone, Dilaudid, methadone, and Percocet); 3 of which reported the concomitant use of other CNS depressants (ie. Ambien, Valium, Xanax, and Zanaflex) and the 4th case did not report a concomitant CNS depressant but had a starting Actiq dose of 1200 mcg 12 – 14 times daily, and experienced confusion, anxiety, vertigo, headache, etc. Subsequently, the dose was decreased to 800 mcg 14 times daily but the events continued. Three of twenty-six cases reported a death outcome (all involving an overdose), 7 reported a hospitalization, and the remaining 13 were reported as medically significant.

It is possible that overdoses or abrupt withdrawal of Actiq could have contributed to the convulsions based on the temporal association; however, a couple of the withdrawal cases were confounded by a past history of seizures and concomitant medications labeled for seizure or decreasing seizure threshold. Convulsions following the use of Actiq have been reported in a long-term extension study in greater than 1% of patients. It is plausible that overdoses and therapeutic doses of Actiq could have contributed to the depressed level of consciousness based on the time course of drug to event. Actiq is labeled for CNS depression and warns of additive CNS depressant effects with the concomitant use of other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcohol.

Psychiatric disorders including drug abuse & dependence (N=31)

Thirty-one cases reported adverse events related to psychiatric disorders and drug abuse/dependence. Notable adverse events are discussed below. Cases may be included in more than one section.

Sixteen cases reported adverse events related to **drug abuse, dependence, and detoxification**. The adverse event terms were coded as: *detoxification (3), drug abuser (6), drug dependence (6), and drug withdrawal syndrome (10)*. Among the indications that were reported, 12 were for non-cancer pain and the remaining 4 were intentional misuse. The duration of Actiq therapy was not well documented but was determined from the narrative of 7 cases and ranged from 1 – 6 years with a median of 3. Four of 14 cases involved an overdose from an intentional misuse by a drug

abuser; one of which reported a death outcome. The remaining 12 of 16 cases involved drug dependence on chronic Actiq therapy for the treatment of pain. The first 3 of twelve cases involved abrupt discontinuation of Actiq secondary to insurance issues and subsequently developed withdrawal symptoms. The 4th – 11th of twelve cases reported undergoing treatment for opioid dependence under the supervision of a physician. The treatments ranged from gradual weaning of Actiq to a hospital admission for rapid medical detoxification (anesthesia assisted). The 12th and final case involved a one day old infant born to a woman who abused Actiq, Norco and heroin during her pregnancy. The infant was reportedly underweight and had underdeveloped lungs in utero, but was born healthy with the exception of withdrawal symptoms which necessitated a five week hospital stay.

Thirteen cases reported other **psychiatric behaviors** coded as: *abnormal behavior (1), agitation (5), anxiety (2), delirium (1), delusion (4), hallucination (4), irritability (4), mental disorder (1), paranoia (2), and thinking abnormal (1).* Eight of 13 cases involved a drug overdose and commonly reported agitation, delusion, hallucination and irritability. Among the 5 remaining cases, 2 reported withdrawal symptoms described as paranoia, 1 reported abnormal behavior indicative of drug dependency, and the last 2 reported anxiety. The age ranged from 19 – 74 years with a median of 48 years (n=13). All 5 cases reported the concomitant use of other opiods; 3 of which reported the use of two opioids in addition to Actiq and the remaining 2 cases reported the use of only one additional opioid. Three of five cases also reported several other concomitant medications; 2 of which reported concomitant medications (ie. atenolol, Effexor, torsemide, Wellbutrin XL and Zonegran) labeled for the specific adverse events that were reported in those cases (ie. anxiety/nervousness and paranoia). None of the 13 cases reported a death outcome, 8 cases reported a hospitalization and the remaining 5 were reported as medically significant.

It is likely that drug abuse and dependence are associated with Actiq because it is a Schedule II controlled substance with abuse liability similar to other opioid analgesics, and is labeled as such in the Actiq prescribing information. It is possible that the following psychiatric behaviors: anxiety, agitation, delusion, hallucination, irritability, and paranoia are associated with Actiq; particularly in cases of overdose and withdrawal. Despite the confounding of the 5 non-overdose cases by other opioids, 2 of which were also confounded by concomitant medications labeled for specific psychiatric events that were reported in the cases, the role of Actiq could not be ruled out. Actiq is labeled for psychiatric behaviors including agitation, anxiety, hallucinations, and thinking abnormal.

5 CONCLUSION

The AERS review of 61 cases did not reveal any notable unexpected safety concerns associated with Actiq. Unlabeled adverse events, including cardiac arrest, ventricular fibrillation, ventricular tachycardia, coma, lethargy, loss of consciousness, delusion, and irritability, were mostly involved with overdoses of Actiq; overdose is labeled for Actiq. Overdoses represented the majority (52%) of serious adverse event cases. Among the overdose cases, 50% were intentional (ie. misuse and suicide), 25% were accidental exposures in young children, 19% involved accidental overdoses, and 6% were of unknown intent. Actiq is labeled for the potential for abuse (legal or illicit) and accidental pediatric exposure with the caution to keep out of the reach of children. Among the cases that did not report an overdose, drug dependence and dental disorders (ie. Dental carries and tooth fracture/loss) were the most commonly reported adverse events; both of which are labeled for Actiq.

6 RECOMENDATION

No labeling or regulatory recommendations are warranted at this time based on the AERS findings. DAEA will continue routine monitoring of adverse events associated with the use of Actiq.

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/s/

Lauren Lee
4/7/2008 10:05:36 AM
DRUG SAFETY OFFICE REVIEWER

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4/7/2008 10:32:55 AM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 8, 2008
To:	FDA Anesthetic and Life Support Drugs Advisory Committee Members (ALSDAC) and FDA Drug Safety and Risk Management Advisory Committee (DSaRM) Members
Through:	Henry Francis, M.D., Deputy Director Office of Surveillance and Epidemiology (OSE)
From:	**OSE Fentora RiskMAP and Postmarketing Review Team** Scientific Lead: Jeanine Best, MSN, RN, PNP, Senior Drug Risk Management Analyst, OSE/DRISK Team Members Kristina Arnwine, PharmD, Acting Safety Evaluator Team Leader, OSE-DMEDP Mary Dempsey, Risk Management Coordinator, OSE-DRISK Darrell Jenkins, Regulatory Project Manager, OSE-IO Claudia Karwoski, PharmD, Acting Director, OSE-DRISK Laura Governale, PharmD, MBA, Drug Use Data Team Leader, OSE-DEPI Lauren Lee, PharmD., Safety Evaluator Team Leader, OSE-DAEA II Kendra Worthy, PharmD, Drug Use Data Analyst, OSE-DEPI
Subject:	Fentora Risk Minimization Action Plan (RiskMAP) and Postmarketing Experience
Drug Name	Fentora (fentanyl buccal tablet)
Application Type/Number:	NDA 21-947/S-005
Applicant/sponsor:	Cephalon
OSE RCM #:	2008-226

This document contains proprietary drug use data obtained by FDA under contract. Contractor approval has been obtained through the FDA/CDER Office of Surveillance and Epidemiology. The drug use data/information has been cleared for release to the public/non-FDA personnel.

CONTENTS

EXECUTIVE SUMMARY

This memorandum provides the Office of Surveillance and Epidemiology's (OSE) preliminary assessment of the performance of the approved Fentora (fentanyl buccal tablet) Risk Minimization Action Plan (RISKMAP) in meeting its risk minimization goals as well as a review of the overall postmarketing experience with Fentora to date. This memorandum encompasses a summary of information provided by the Sponsor regarding the Fentora RiskMAP experience, and data available to FDA including drug use data and adverse events (overall safety and medication errors). This summary was requested in preparation for the May 6, 2008 Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting on an expanded indication of use for Fentora.

A RiskMAP was approved at the time of the initial FDA approval of Fentora as an important part of its postmarketing risk management to, 1) minimize the use of Fentora by opioid non-tolerant individuals, minimize misuse of Fentora, and minimize unintended (accidental) exposure to Fentora. The RiskMAP consisted primarily of healthcare provider and patient education on about the risks and benefits of Fentora, a reporting and data collection system for safety surveillance, and a plan to monitor, evaluate, and determine the incidence of use of Fentora by opioid non-tolerant individuals, misuse of Fentora, and unintended (accidental) exposure to Fentora. Despite the implementation of the RiskMAP, there has been the need for stronger labeling with an emphasis on key safety information and enhanced drug communication efforts in the form of Dear Doctor and Dear Healthcare Professional Letters, Public Health Advisory, and Healthcare Information Sheet, because postmarketing data continues to trend away from safe use of the product particularly in patients are who being treated with Fentora outside of the limited labeled indication.

Fentora use has increased more than five-fold since the initial 1st quarter launch in September 2006, with most use occurring off-label in non-cancer pain indications, and a significant amount of use occurring in opioid non-tolerant individuals (in year 2007, approximately 59% of patients who filled a prescription for Fentora were on concurrent therapy with a product from the pain market.[1]). The review of Fentora postmarketing adverse event cases did not reveal any notable unexpected safety concerns. Improper use and medication errors account for more than two-thirds of the adverse events reported with Fentora. The majority of these adverse events occurred when patients were being treated for off-label uses for Fentora, such as back pain, chronic/non-cancer pain, and migraines. Medication errors include conversion errors between Actiq and Fentora, improper frequency of administration, wrong route of administration, wrong drug dispensed, improper administration technique, accidental exposure, and accidental overdose.

Based on our review of the postmarketing experience with Fentora, we do not believe the RiskMAP has been effective in minimizing the risks it was developed and implemented to minimize. Cephalon states in their approved RiskMAP that, "interventions will be instituted as warranted as follow-up to surveillance and monitoring activities."[2], but they have never submitted information that interventions and/or adjustments were proactively considered or instituted to address RiskMAP goal failures, in particular for the failure of RiskMAP Goal # 1, that Fentora should be used only by opioid tolerant patients with cancer; a goal that has

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[1] Worthy K, Governale L, Division of Epidemiology. Concurrency Analysis VOCON: Fentora or Actiq with Pain Market Products, April 1, 2008

[2] Fentora (fentanyl buccal tablet) CII, Risk Management Plan, submitted September 19, 2006 to NDA 21-947, approved September 25, 2006

consistently failed since the launch of Fentora. Instead, Cephalon uses the large extent of product off-label use which reflects the failure of RiskMAP Goal #1, to justify the proposed expanded indication for Fentora. Expanding the Fentora indication as proposed will most likely amplify and exacerbate the adverse event trends and use patterns (including use in opioid non-tolerant individuals) we have already observed. Additional risk minimization strategies to ensure the safe and appropriate use of Fentora should be implemented and evaluated for effectiveness with the current limited cancer indication, where the benefits outweigh the risks before expanding use to a broader population.

1 BACKGROUND

1.1 INTRODUCTION

Fentora is a Schedule II, potent, rapid-onset opioid analgesic in a buccal tablet form intended for transmucosal delivery. A Fentora dose is readily absorbed with 50 percent of the fentanyl dose initially absorbed transmucosally and the rest swallowed, with prolonged absorption through the gastrointestinal tract.[3] Fentora is the second approved oral transmucosal fentanyl product approved for use in the U.S. (Actiq was approved in 1998). Fentora is more bioavailable than Actiq (65% versus 47%) and, therefore, is not equivalent on a microgram per microgram basis with Actiq (or other fentanyl-containing products). Fentora is available in five dosage strengths, 100, 200, 400, 600, and 800 micrograms; some of these strengths overlap with Actiq dosage strengths.

Fentora has the usual opioid safety concerns including abuse, misuse, and diversion but it also has the additional safety concern of fatal respiratory depression with accidental exposure in children (at any dose) and with use in opioid naïve (non-tolerant) [4] patients.

1.2 REGULATORY HISTORY

Fentora (fentanyl buccal tablet) received approval September 25, 2006, "for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain",[5] (revised February 7, 2008, to, "only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain").[6]

The RiskMAP was approved at the time of the initial FDA approval of Fentora as an important part of its postmarketing risk management to, 1) minimize the use of Fentora by opioid non-tolerant individuals, minimize misuse of Fentora, and minimize unintended (accidental) exposure to Fentora. Required RiskMAP components included:[7]

1. Implementation of a program and distribution of materials to educate prescribers, pharmacies, nurses, and patients about the risks and benefits of Fentora.

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[3] Fentora (fentanyl buccal tablet) Label, February 7, 2008

[4] Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily or a week or longer (from approved Fentora label).

[5] Fentora Prescribing Information Approved September 25, 2006

[6] Fentora Prescribing Information, revised February 7, 2008

[7] Approval Letter, NDA 21-947, Fentora (fentanyl buccal tablet), September 25, 2006

2. Implementation of a reporting and data collection system for safety surveillance.
3. Implementation of a plan to monitor, evaluate, and determine the incidence of use of Fentora by opioid non-tolerant individuals, misuse of Fentora, and unintended (accidental) exposure to Fentora.

Reports of death and life-threatening side effects were reported to the Agency in early September 2007. These reports of death and life-threatening side effects occurred in patients who: 1) should not have been prescribed Fentora (patients who did not have cancer and/or were not opioid tolerant); 2) were prescribed the wrong Fentora dose; and 3) took too many Fentora doses. There were also reports of healthcare professionals who substituted Fentora for another fentanyl-containing product. In response to these reports, the Sponsor issued a "Dear Doctor Letter" and "Dear Healthcare Professional Letter" on September 10, 2007, to inform healthcare providers about key safety information regarding the use of Fentora, including appropriate patient selection, and proper dosing and administration. Additionally, FDA issued a Public Health Advisory: "Important Information for the Safe Use of Fentora (fentanyl buccal tablets)"[8] and a Healthcare Information Sheet on September 26, 2007.

Revised labeling including the Prescribing Information, Medication Guide, and Carton labels to reflect the enhanced key safety information was approved February 7, 2008.

Cephalon submitted an Efficacy Supplement (S-005) on November 9, 2007, to expand the Fentora indication to "the treatment of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying chronic pain"[9], and to allow for sublingual product use. Cephalon justifies the need for this expanded indication from postmarketing reports of substantial off-label use of Fentora in patients for relief of chronic non-cancer-related breakthrough pain.[10] This Efficacy Supplement (S-005) is the subject of the May 6, 2008, FDA Advisory Committee Meeting.

1.3 RISK MINIMIZATION ACTION PLAN (RISKMAP)

Cephalon uses their SECURE (Solutions through Education, Communication, and Understanding Risk Minimization Excellence) Program (educational interventions and tools) to minimize the risks identified for Fentora. The goals of the program are: [11]

1. Fentora should be used only by opioid tolerant patients with cancer.
2. Abuse, misuse and diversion of Fentora should not occur.
3. Unintended (accidental) exposure to Fentora should not occur.

The key Fentora RiskMAP strategies are:

- **Labeling**
  - Package Insert (PI) with Boxed Warning emphasizing the key safety messages (for prescribers and pharmacists)
  - Medication Guide (MG). The Medication Guide for patients contains information for the safe and effective use of the product for patients. This information is consistent

[8] FDA Public Health Advisory: Important Information for the Safe Use of Fentora (fentanyl buccal tablets), September 26, 2007

[9] Cover Letter, NDA 21-947/S-005, Fentora (fentanyl buccal tablet) CII, November 9, 2007

[10] Fentora (fentanyl buccal tablet) CII, Risk Management Plan, submitted November 9, 2007 to NDA 21-947/S-005

[11] Fentora (fentanyl buccal tablet) CII, Risk Management Plan, September 19, 2006

with the key messages provided in the PI, but is written in consumer-friendly language.

- Blister – double foil blister that meets requirements for child resistance (for patients)
- Blister label – includes warnings that Fentora should be kept out of the reach of children and that it is only for patients already taking opioids (for patients)
- Carton label – includes a reminder checklist to prompt the pharmacist to counsel the patient about important risks and directs the patient to read the Medication Guide for important warnings (for pharmacists and patients)

- **Education/Communication/Outreach Program (includes labeling) and the following:**
  - Direct Risk Communication by Cephalon Field Representatives
  - Educational Introductory Letter to Healthcare Professionals PharmAlert (for pharmacists)
  - Physician Education for Pain Centers of Excellence
  - Pharmaceutical Compendia
  - Counseling messages/Consumer Medication Information
  - Counseling Aids/Brochures
  - RiskMAP Speaker Training
  - Training for Cephalon Field Representatives
  - Independent Continuing Medical Education (CME) – targeted to likely prescribers of Fentora
  - Introductory letter to Drug Diversion Authorities
  - Physician and Pharmacist Education – directed to "geographic hotspots" that focus on preventing/minimizing misuse, abuse, and diversion
  - Physician Education - targeted to members of professional societies
  - Fentora Website (for healthcare professionals and patients) – provide education about the three major risks associated with Fentora
- **Distribution via Controlled Substance Act (CSA) for Schedule II products:**
  - CSA Schedule II distribution controls and recordkeeping consistent with other Schedule II substances are in place for Fentora. Federal and State regulations govern the manufacturing, distribution, prescribing, dispensing, storage, and disposal of Schedule II products.
  - Prescriptions must be handwritten and no refills are allowed.

Comment: *Revisions to the education plan are currently under consideration but the majority of these submitted materials appear more product "promotional" than educational (targeted to the RiskMAP goals).*

- **Surveillance Plan, including both spontaneous reporting and active surveillance:**
  - **Active Monitoring:** The Sponsor monitors reports of abuse and diversion from the following databases. Signals generated will trigger an exam and follow-up from Cephalon.

- The Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS)[12]
- Rocky Mountain Poison and Drug Center (RMPDC)
- Toxic Exposure Surveillance System (TESS)
- Drug Abuse Warning network (DAWN) and DAWN LIVE!

- **Post-Marketing Reporting Systems:** The Sponsor follows-up on any reports of adverse drug reactions associated with Fentora and will comply with all reporting requirements described in 21 CFR 314.80 and 314.81. 15-Day reports currently submitted to FDA for the following events:
  - Serious adverse drug reactions associated with suspected abuse, misuse, or diversion;
  - Any report with an outcome of death;
  - All accidental exposures including asymptomatic reports;
  - Any report in a child or adolescent (ages 0-16), whether or not the exposure was intended, and regardless of the outcome;
  - All actual and potential medication error reports regardless of patient outcome.

- **Evaluation Plan/Interventions arising from periodic evaluations of surveillance and monitoring activities:**
  - Surveys: Surveys are used to measure knowledge, attitudes, and behaviors associated with the Fentora RiskMAP. Three separate surveys are used that individually target prescribers, pharmacists, and patients.
  - Patient Longitudinal Dispensing Data: Longitudinal data is purchased from data vendors to assess the concomitant prescribing of Fentora with another opioid medication.
  - Interventions: Interventions will be instituted as warranted as follow-up to surveillance and monitoring activities. Interventions will mainly consist of education or community outreach.

1.3.1 RiskMAP Report Submissions

Fentora RiskMAP reports are supposed to be submitted quarterly for the first two years after approval and annually thereafter. The data incorporated into these reports includes:

1. Extent of use (denominator estimates);
2. Indicators of off-label use, inappropriate prescribing (i.e., opioid-naive), inclusive of patient longitudinal data (note: summarization of all non-accidental pediatric exposures not associated with an ADR will be included here);
3. Summarization of reports involving all medication errors, regardless of patient outcome;
4. Summarization of all accidental exposures (in children and adults);

[12] RADARS® calculates the rates of prescription opioid abuse on a quarterly basis for each 3-digit zip code in the U.S. The calculation is based on population and unique individuals that have filled a prescription. RADARS® system studies include 1) Poison Centers, 2) Drug Diversion 3) Key Informant, and, 4) Methadone Clinics.

5. Summarization of all non-accidental pediatric exposures associated with an ADR (serious and non-serious)
6. Summarization of adverse events involving opioid naïve patients;
7. Rates of suspected misuse, abuse, addiction or diversion reported;
8. Results of any investigation or surveys conducted, and;
9. Outcomes from any interventions, such as targeted educational interventions and anti-diversion programs conducted.[13]

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

2.1.1 Documents

The following documents were reviewed in the preparation of this review:

- Fentora (fentanyl buccal tablet) CII, Risk Management Plan, submitted November 9, 2007 to NDA 21-947/S-005
- Fentora (fentanyl buccal tablet) CII, Risk Management Plan, submitted September 19, 2006 to NDA 21-947, approved September 25, 2006
- Amwine K., Division of Medication Errors: Medication Error Postmarketing Safety Review, April 4, 2008
- Worthy K, Governale L, Division of Epidemiology, Concurrency Analysis VOCON: Fentora or Actiq with Pain Market Products, April 1, 2008
- Fentora Approval Letter, NDA 21-947, September 25, 2006
- Fentora RiskMAP Report (1st Quarter – 9/25-06-12/31/06) submitted April 13, 2007
- Fentora RiskMAP Report (2nd Quarter – 1/1/07-3/31/07) submitted July 20, 2007
- Fentora RiskMAP Report (3rd Quarter – 4/1/07-6/30/07) submitted October 12, 2007
- Fentora RiskMAP Report (4th Quarter – 7/1/07-9/30/07) submitted February 26, 2008
- FDA Public Health Advisory: Important Information for the Safe Use of Fentora (fentanyl buccal tablets), September 26, 2007, available at: http://www.fda.gov/cder/drug/advisory/fentalyn_buccal.htm
- Fentora approved labeling, revised February 7, 2008, available at http://www.fda.gov/cder/foi/label/2008/021947s006lbl.pdf

2.1.2 Drug Utilization Data Sources

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined nationally projected estimates of the number of prescriptions for Fentora®, (fentanyl citrate), NDA 21-947, as well as other fentanyl products for years 2000 through 2007 using Verispan, LLC: Vector One®: National (VONA) (see Appendix 1 for full description). In addition, we examined dispensed prescriptions for Fentora® by patient age for calendar years 2006-2007. We also utilized Verispan's Total Patient Tracker (TPT) to obtain nationally

[13] Fentora RiskMAP, NDA 21-947, September 19, 2006

projected estimates of the number of patients who received a dispensed prescription for Fentora® in outpatient retail pharmacies for calendar years 2006-2007. Utilization in inpatient and mail order pharmacies were not examined.

2.1.2 Selection of Adverse Event (AE) Cases in AERS*

On February 25, 2008, the Adverse Event Reporting System (AERS) database was searched using the trade name, Fentora, for all adverse event cases that were reported to the Agency since drug marketing (September 25, 2006). The cases were individually reviewed and duplicates were consolidated.

2.1.3 Selection of Medication Error Cases in AERS*

On March 18, 2008, the FDA Adverse Event Reporting System (AERS) database was searched to identify post-marketing reports of medication errors associated with Fentora. AERS was searched using the trade name "Fentora", verbatim search term "Fentor" without reference to any MedDRA terms. Reports were reviewed for duplicates and grouped together as cases.

2.1.4 Institute of Safe Medication Practices Outpatient Medication Errors**

Upon our request, the Institute for Safe Medication Practices (ISMP) searched their database for outpatient medication errors involving Fentora. The Institute of Safe Medication Practices Outpatient Medication Errors databases search did not identify any additional cases of medication errors associated with Fentora.

2.2 ANALYSIS TECHNIQUES

This section provides details on data used and our methods of analysis.

2.2.1 Analysis of Drug Utilization Data

For drug use analysis we examined nationally projected estimates of the number of prescriptions for Fentora®, (fentanyl citrate), NDA 21-947, as well as other fentanyl products for years 2000 through 2007 using Verispan, LLC: Vector One®: National (VONA) (see Appendix 1 for full description). In addition, we examined dispensed prescriptions for Fentora® by patient age for calendar years 2006-2007. We also utilized Verispan's Total Patient Tracker (TPT) to obtain nationally projected estimates of the number of patients who received a dispensed prescription for Fentora® in outpatient retail pharmacies for calendar years 2006-2007. Utilization in inpatient and mail order pharmacies were not examined.

2.2.2 Analysis of Adverse Event Data including Medication Errors

The adverse event reporting system database (AERS) is a voluntary reporting system for manufacturers, health care professionals, and consumers to report adverse events for approved drugs and therapeutic biologics. Due to the voluntary system, there is underreporting and also duplicate reporting of adverse events. For any given report, there is no certainty that the reported

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* Note that AERS was search for all Fentora Adverse Events on February 25, 2008, and again on March 18, 2008 for reports with medication errors.

** The Institute of safe Medication Practices medication errors contains confidential and proprietary data, which cannot be shared outside the FDA.

suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues.

3 RESULTS

This section presents the results of our analysis of postmarketing data for Fentora from drug utilization data sources, AERS, and Fentora RiskMAP Reports.

3.1 DRUG UTILIZATION: TOTAL DISPENSED PRESCRIPTIONS

Findings should be interpreted in the context of the known limitations of the databases used. Data from Verispan's Vector One®: National and Total Patient Tracker do not include data on over-the-counter products, mail order prescriptions, or drug utilization patterns in clinics.

Table 1 and Figures 1 and 2 in Appendix 2 show the total number of dispensed prescriptions for fentanyl products from U.S. retail pharmacies for years 2000-2007. In year 2005, Fentanyl Transdermal surpassed Duragesic® as the most dispensed fentanyl product. In year 2007, prescriptions dispensed for Fentora® ranked 4th among fentanyl products with approximately 90,751 (2%) prescriptions dispensed.

Between years 2006 and 2007, there was approximately a 79% decrease in Actiq® prescriptions dispensed and approximately 500% and 521% increase in prescriptions dispensed for Oral Transmucosal Fentanyl & Fentora®, respectively (Figure 2, Appendix 2). Dispensed prescriptions for Fentora® increased from approximately 14.6 thousand in year 2006 to nearly 91 thousand in year 2007.

3.2 DRUG UTILIZATION: DEMOGRAPHIC DATA

Table 2 in Appendix 2 shows the total number of retail prescriptions for Fentora® dispensed in years 2006-2007. During that time period, the majority (approximately 68%) of prescriptions dispensed in outpatient retail pharmacies for Fentora® are for patients aged 41-65 years old. Patients aged 26-40 years old followed with approximately 23% of dispensed prescriptions for Fentora® for years 2006-2007. Prescriptions for Fentora® dispensed to pediatric patients age 0-16 years old comprised less than 1% of all Fentora® prescriptions dispensed in years 2006-2007.

Table 3 in Appendix 2 shows the number of *patients* that received a dispensed prescription for Fentora® during years 2006-2007. Trends for patient data are similar to that of prescription data, with the majority of patients aged 41-65 and 26-40 years old filling Fentora® prescriptions.

3.3 ADVERSE EVENTS CASES

3.3.1 Summary of Adverse Event cases

The table below presents the number of adverse event cases retrieved from the AERS database and the number of cases that were included in the final review after exclusions:

Table 1. Selection of Individual AERS Cases			
Drug Name	**Crude Counts**	**Cases Excluded (N=23)**	**Number of Cases Included**
Fentora	42	• Reports of actual/potential medication errors with no adverse event cited (16) [14] • Reports of death without any specific patient information (3) • Reports with adverse event not related to Fentora per reporter (2) • Report of product complaint with no adverse event cited (1) • Report of death from natural causes (1)	19

Nineteen AERS cases were included in this case series. The reported adverse events in these cases were categorized according to the AERS system organ class (SOC) as listed below *(a report may contain more than one adverse event term)*:

Table 2. List of adverse events (Preferred Terms) categorized into System Organ Classes (SOC)	
System Organ Classes	**Preferred Terms**
Cardiac disorders (1)	acute myocardial infarction (1)
Gastrointestinal disorders (2)	retching (1), constipation (1)
General disorders and administration site conditions (14)	lack of efficacy (6), application site bleeding (2), application site bruising (1), application site ulcer (1), application site pain (1), application site burning (1), flushing (1), hyperhidrosis (1)
Injury, poisoning and procedural complications (18)	medication errors (10), intentional overdose (2), overdose (2), accidental overdose (2), intentional drug misuse (2), accidental exposure (1)
Metabolism and nutritional disorders (1)	oral intake reduced (1)
Nervous system disorders (7)	somnolence (3), loss of consciousness (2), cerebrovascular accident (1), dysarthria (1)
Psychiatric disorders (4)	drug dependence (1), suicidal attempt (1), suicide (1)
Renal and urinary disorders (1)	dysuria (1)
Respiratory, thoracic and mediastinal disorders (2)	respiratory arrest (1), dyspnea (1)
Vascular disorders (1)	dizziness (1)

[14] See Medication Error Section for a complete analysis of all medication error reports, including the reports with or without a resulting adverse event.

A chart summary of the demographics and characteristics of the 19 adverse event cases associated with Fentora are summarized below:

Table 3. Summary of Demographics and Characteristics of AERS Fentora Cases (N=19)				
Sex	Male -9, Female -10			
Age (n=16)	Range 16-73 years, Mean 43 years, Median 43.5 years			
Indication	Cancer pain -1	Unspecified - 1		
	Non-cancer pain – 11 • Bone pain -1 • Chronic back pain -2 • Chronic pain-2 • Mandibular joint pain -1 • Migraine -2 • Migraine and back pain -1 • Spinal injury -1 • Unspecified brain condition -1	Misc - 6 • Abuse -2 • Intentional overdose -2[15] • Suicidal attempt – 1 • Completed suicide -1 • Accidental exposure -1		
Dose	Estimated total daily dose mentioned (6) – Range 600-3200 mcg, Median 2000 mcg			
	Total daily dose unknown (3)			
	Misc. (10) • Suicide/suicidal attempt (2) • Intentional overdose (2)[16] • Accidental overdose (2) • Accidental exposure (1) • Intentional misuse (2) • Overdose (2)[17] • Incorrect dispensing of Fentora for Actiq (1)			
Time to onset (N=11)	Range- immediately - 5 months, Median – 8 days • Same day – 5 *(e.g. immediately, 1 dose, same day, shortly after taking, 1 day)* • 8 days -2 • 1 month -2 • 40 days-1 • 4-5 months - 1 • Unspecified- 8			
Other Concomitant Medications (N=13)	Actiq -1	Dilaudid -1	Lortab -1	Soma -1
	Allegra -1	Duragesic - 2	Lyrica -1	Tenormin -2
	Ambien -2	ETOH -1	Maxidex -1	Tegretol -1
	Avinza -1	Fentanyl Patch -3	Morphine -2	Trazodone -1
	Bisoprolol -1	Flomax -1	Opana -1	Trileptal -1
	Celebrex -1	Fosamax -2	Oxycontin -3	Tylenol -1

[15] One of 2 intentional overdose cases also reported suicide.
[16] One of 2 intentional overdose cases also reported suicide.
[17] One of 2 overdose cases also reported intentional misuse.

Table 3. Summary of Demographics and Characteristics of AERS Fentora Cases (N=19)				
	Clonazepam -1	HCTZ -1	Prevacid -2	Wellbutrin- 1
	Diazepam -1	Lidoderm -1	Rapamune -1	Xanax -1
Drug Levels (N=2)	Fentanyl 14.1 ng/mL & 17 ng/mL			
Outcomes	Death	5		
	Life Threatening	1		
	Hospitalization	1		
	Other (medically serious)	3		
	Unspecified	9		
Dec/Rechallenge	Positive dechallenge -3			
Year (Event Date)	2006	2		
	2007	13		
	2008 (1/1 - 2/25)	1		
	Unspecified	3		
Year (Receipt Date)	2007	17		
	2008 (1/1 – 2/25)	2		
Reporter Type	Healthcare professional	9 (MD-7, DO-1, RN-1)		
	Consumer	8		
	AAPCC[18]	2		
Type of Report	15-Day	19		
Report Source	US- 19			

3.3.2 Review of Selected Individual Adverse Events

As shown in Table 3, 19 domestic cases were included in this cases series. The age of patients ranged from 16 to 73 with the mean of 43 years. Gender was almost evenly divided between males (10) and females (9). Fentora was most commonly used for non-cancer pain (58%), followed by abuse (11%), suicidal attempt (11%), intentional overdose (11%), cancer pain (5%), accidental exposure (5%), and unknown (5%); it is noteworthy that Fentora was used for an approved indication (cancer pain) in only 1 case. Excluding ten cases of overdoses, accidental exposure, suicidal attempt, and/or intentional misuse, the total daily dose was mentioned in 6 of 9 cases, ranging from 600 to 3200 mcg with the median of 2000 mcg. In these 9 cases, 4 patients switched from Actiq to Fentora; in at least 2 of 4 cases, the patients were converted on a mcg per mcg basis from Actiq to Fentora due to a prescribing error, despite the labeling warning to avoid this direct conversion. The switch from Actiq to Fentora was made due to cost and dental issues,

[18] American Association of Poison Control Centers

respectively, in 2 of 19 cases. In 6 of 19 cases, the patients were likely opioid tolerant.[19] Only one case specified that the patient may not have been taking "around-the-clock" opioid medications as prescribed. It was not possible to determine the tolerance in the remaining cases due to the limited information available. Eleven of 19 cases reported the concomitant use of another opioid product.

Time to onset was reported in 11 cases and ranged from *immediate* to 5 months with the median of 8 days; this time period was calculated from the first day of starting Fentora to the date of the event. Most of the reported events were mentioned in only one report, except for medication errors (10), lack of efficacy (6), somnolence (3), application site bleeding (2), intentional overdose (2), overdose (2), accidental overdose (2), intentional drug misuse (2), and loss of consciousness (2). Notable unlabeled events included acute myocardial infarction, cerebrovascular accident, dysarthria, and dysuria. Expected adverse events such as overdose (intentional/accidental), accidental ingestion, drug dependence, misuse, somnolence, dyspnea, retching, dizziness, application site reaction (bleeding/pain/bruising/ulcer/burning), constipation, reduced oral intake, hyperhidrosis, respiratory failure, impaired consciousness, and flushing were also reported. Thirteen of 19 cases reported the concomitant use of other medications in addition to Fentora. Outcomes included death (5), hospitalization (1), life-threatening (1), other medically serious (3), and unknown (9).

Clinically significant events and notable groupings of selected reactions are discussed in more detail below[20]:

3.3.2.1 Deaths (n=5)

Five cases reported a death outcome. The causes of death were accidental fentanyl overdose (2), metastatic leiomyosarcoma (1), suicide (1), and unknown (1).

The two accidental overdoses involved a 34 year old and a 40 year old female who were prescribed Fentora for migraine and chronic back pain, respectively. The first patient had a high tolerance to opioids given the high doses of both Actiq and Demerol required to relieve her pain, and the second patient had been taking Duragesic 50 mcg/hr prior to and during Fentora therapy. Both cases involved a medication error at the pharmacy level. In the first case, the physician was told by the patient's husband that he thought the dispensed instructions stated that Fentora could be taken every 30 minutes, but the physician could not verify this information. Six Fentora tablets were missing (2400 mcg total) and were presumed to have been consumed by the patient. The autopsy revealed a blood fentanyl level of 14.1 ng/ml, and the patient's death was ruled as an accidental fentanyl overdose. In this case, it is noteworthy that the patient had a history of depression, and according to the physician, the patient claimed to be suicidal without any indication of suicidal thought. In the second case, the patient informed the physician of her plans to travel out of town, and the physician wrote a second prescription for Fentora with instructions to the pharmacy not to fill until a specific date. It was later discovered that the second prescription was filled earlier than stated on the prescription. The patient had died during her travel out of town. This patient's blood fentanyl level was 17 ng/mL. The only abnormal autopsy finding involved the heart in which a 70% focal stenosis of the anterior descending coronary artery was discovered. The autopsy determined the cause of death as accidental acute fentanyl toxicity with coronary atherosclerotic disease as a contributing factor.

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[19] Opioid tolerance is defined as at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid daily for a week or longer for their underlying persistent pain prior to Fentora therapy. *(Fentora Package insert 2007 Cephalon, Inc.)*

[20] A case can contain multiple adverse events, and therefore may be included in more than one section.

The death in the third case was related to the underlying metastatic leiomyosarcoma and not related to the Fentora therapy according to the reporting physician. The other reported adverse events in this case included dysarthria, dysuria, somnolence, constipation, reduced oral intake, and lack of efficacy; however, the reporter stated that only dysarthria, dysuria, somnolence, and constipation were partly associated with the effects of opioid therapy, especially since high doses of both buccal and transdermal fentanyl were used by the patient. The other events were more closely related to the underlying cancer. The fourth case described an intentional overdose of Fentora involving a male in his 40s-50s with a history of drug addiction. He stole 25 Fentora tablets from his partner (who had been taking it for cancer pain) and ingested them in an apparent suicide. The fifth case involved a male patient (age unknown) who stole his wife's Fentora and experienced an overdose. He went to the ER where he was diagnosed with an acute myocardial infarction. This patient left the ER against medical advice and returned home where he later died. No further information was provided.

***Comments**: The above cases provided evidence to show that 3 of 5 deaths (accidental OD-2, suicide-1) were related to the use of Fentora. The autopsies for the 2 accidental overdose cases stated that the cause of death was fentanyl toxicity. Although it is noteworthy that one of the 2 patients had a history of depression and possibly claimed to be suicidal, the reporting physician stated that there was no indication of suicidal thought, and therefore making the possibility of suicide less likely. In both cases, the safety concern is the medication error that may have occurred at the pharmacy level, especially since this product has a RiskMAP with an education component for pharmacists to prevent such errors. The safety concern regarding the suicide case is that a large number of Fentora tablets was readily available for this patient; although it is impossible to prevent suicide from occurring, this case illustrates that despite the efforts to reduce drug diversion through a RiskMAP for this product, it is still possible to access this drug for self-harm. The same concern can be applied to the patient who stole his wife's Fentora and experienced acute myocardial infarction. Although in this case, there wasn't enough evidence to show that this patient's MI and death were directly related to Fentora use, we cannot rule out the possibility that the overdose of Fentora could have contributed to his death in the absence of proper medical treatment.*

3.3.2.2 Medication Errors (n=10)

Ten cases described medication errors associated with an adverse event. The medication errors involved prescribing errors, pharmacy dispensing errors, incorrect route of administration, and inappropriate frequency of use in these cases. *See **Medication Error Analysis** section of this review for a complete analysis of all medications errors, including potential/actual errors that did not lead to an adverse event (n=16; excluded from AE analysis) and medication errors associated with an adverse event (n=10).*

3.3.2.3 Injury, Poisoning, and Overdoses (n=8)

Eight cases reported adverse event terms related to a drug injury, poisoning, and/or overdose. The cases were grouped into the following categories: overdose (2), intentional overdose (2), accidental overdose (2), intentional drug misuse (2), and accidental exposure (1); one case reported both overdose and intentional drug misuse.[21] Outcomes included death (4), life-threatening (1), other (2), and unknown (1).

[21] Suicide cases are discussed separately in a later section.

Two reports described an **accidental overdose** and one case described an **accidental exposure**. The two accidental overdoses were previously discussed in the *Death* section where two patients died from fentanyl toxicity; both cases involved a medication error at the pharmacy level (see *Death* section). The accidental exposure case involved a 73 year old female with Alzheimer's disease who mistakenly ingested 2 Fentora tablets thinking that it was aspirin because the Fentora tablets were placed in an unlabeled container. She subsequently experienced flushing and sweating. The paramedics arrived and discovered 6 Lidoderm patches on her skin; she was transported to the ER and treated for symptoms presumed to be due to lidocaine overdose because the ER physician was unaware that she had accidentally ingested Fentora. Pt responded quickly to treatment and was released.

Two reports described an **intentional overdose**. One of 2 intentional overdose cases was discussed in the *Death* section and involved a suicide. The second intentional overdose case involved a 34 year old female who overdosed by taking 1/3 of a box of Fentora (8000 mcg) all at once. She subsequently experienced loss of consciousness and was taken to the ER. She recovered and was seeking treatment for abuse.

Two cases described an **intentional drug misuse**. The first case was discussed in the *Death* section and involved a male patient (age unknown) who stole his wife's Fentora and experienced an **overdose** and acute MI. The second case involved a 36 year old male who intentionally abused an undisclosed amount of Fentora and experienced drowsiness, lethargy, and dyspnea. No further information was provided in this case.

Two cases described an **overdose**. The first case was the death case described in the previous paragraph under intentional drug misuse. The second case involved a 34 year old female with a history of severe neck injury, trigeminal neuralgia, and migraines. She was switched from Actiq to Fentora due to cost, and on an unspecified date, she experienced respiratory arrest and loss of consciousness soon after taking a dose of Fentora. Although her concomitant medications included Oxycontin, Lortab, Ambien and clonazepam, she had only taken Fentora when the events occurred. She was transported to a hospital via the paramedics, who administered Narcan. She was later released from the hospital. The report noted that she would have died if she was not discovered by her roommate in time. Although the patient was described by the physician as being 'opioid tolerant,' the physician's review of his office notes indicated that this patient may not have been taking around-the-clock medication as prescribed. The patient is now back on Actiq.

Comments: In all cases, the reported adverse events were related to the use of Fentora. In the accidental overdose and exposure cases, it is possible that the events could have been prevented if there was no pharmacy error or if the Fentora tablets were better stored in the home. The intentional overdoses and drug misuse cases show that drug diversion is occurring despite a RiskMAP for Fentora to minimize these events. The last case of overdose illustrates the importance of patient selection, requiring around-the-clock opioid use prior to Fentora, since overdoses can occur even in patients who are not opioid-naïve.

3.3.2.4 Lack of Efficacy (n=6)

Six cases reported that Fentora was not effective at treating cancer pain (1) and non-cancer pain (5); the off-label indications included bone pain, unspecified nervous system disorder, mandibular joint pain, chronic back pain, and spinal injury related pain. The one case involving cancer pain is the same case that was described in the *Death* section involving a 64 year old female who died due to the underlying metastatic leiomyosarcoma. This patient was never able to achieve adequate pain control while taking Fentora (400 mcg q2 hrs prn up to 8 times daily) until he underwent insertion of a neurostimulator implant, at which time Fentora was discontinued; this patient was also concomitantly taking four 50 mcg/hr transdermal fentanyl.

Among the 5 cases that reported off-label uses of Fentora, 3 cases reported lack of efficacy without any other adverse event. In the first case, the patient switched from Actiq 2400 mcg/d for bone pain to Fentora; the patient was also concomitantly taking transdermal fentanyl (250 mcg/hr). The patient required 100 mcg of Fentora every hour but still had no pain relief; the physician increased the dose to 200 mcg, and no further information was provided. In the second case, the patient who was taking Actiq 800 mcg for an unspecified nervous system disorder was switched to Fentora 800 mcg due to dental issues; the patient was also taking Avinza concomitantly. Although Fentora has greater bioavailability than Actiq when comparing mcg per mcg basis, no adverse event was reported in this patient; the patient was switched back to Actiq due to the lack of pain relief. The third patient who was taking Opana, morphine, and MsContin for mandibular joint pain was prescribed Fentora sublingually (rather than buccally) due to her underlying mouth pain. The patient noted that the tablet did not dissolve within a normal amount of time, and therefore, she subsequently experienced lack of effect. According to the reporter, Fentora was not discontinued, despite the lack of efficacy; she noted that her dry mouth from her underlying oral condition could have contributed to the dissolution problem.

The remaining 2 of 5 lack of efficacy cases reported dizziness and application site burning/bleeding, respectively. Dizziness was reported in a patient who received Fentora instead of Actiq due to a pharmacy dispensing error; Fentora was placed in a box along side Actiq lozenges with the note that stated "generic." Dizziness subsided but the patient reported no pain relief of her chronic back pain. The last case also involved a medication error (prescribing error) where the patient was switched from Actiq 600 mcg to Fentora 600 mcg; the labeling for Fentora specifies that these two drugs are not bioequivalent and should not be converted on a mcg per mcg basis. This patient experienced application site burning/bleeding and no pain relief. He was switched back to Actiq, and the application site reactions resolved.

Comments: *In 5 of 6 cases, Fentora was used off-label; since Fentora is not FDA approved for non-cancer related indications, we could not conclude that there was an issue of lack of efficacy with Fentora in these cases. The one remaining case involving cancer pain reported that the typical side effects of opioids (e.g. constipation, somnolence, dysuria, & dysarthria) limited the amount of Fentora use per day, which could have contributed to the lack of pain relief. This case did not suggest that there was an issue of lack of efficacy with Fentora when used properly. From a safety perspective, however, it is concerning that in 3 of 5 off-label use cases, there was an incorrect conversion from Actiq to Fentora (2) or that Fentora was considered a generic version of Actiq (1); Fentora is not bioequivalent to Actiq on a mcg to mcg basis. In patients who are not opioid tolerant, these types of medication errors could have a serious outcome.*

3.3.2.5 Application Site Reactions (n=3)

Three cases reported application site reactions including bruising, ulceration, bleeding, and/or burning temporally associated with the use of Fentora. In two cases, a positive dechallenge was reported, and in the third case, Fentora therapy was continued. The first case of positive dechallenge was previously described as the last case in the *Lack of Efficacy* section. This case involved a 51 year old male who experienced application site burning and bleeding after 8 days of Fentora use (600 mcg QID), but the events resolved approximately 2 days after discontinuing the drug. In the second case, a 48 year old female experienced multiple application site ulceration of the gums shortly after initiating Fentora for migraines and back pain, despite rotation of the sites. The physician suggested sublingual use and her tongue subsequently became ulcerated and was bleeding from the tip. Fentora was discontinued and the ulcers resolved. One month later, Fentora was restarted, and the patient developed ulcerations and bleeding while taking the 400 mcg dose; however, the reporter indicated that the patient did not experience these events while taking the 200 mcg or the 600 mcg doses. Fentora therapy was discontinued and the events resolved. The reporting physician indicated that the patient had an apparent idiosyncratic hypersensitivity to

something in Fentora, and that the events are unlikely related to Fentora therapy. In the last case, a 45 year old female reported application site bruising (redness and tenderness) after approximately 8 days of Fentora use (200 mcg q8hrs) for chronic pain. It is noteworthy that this patient had accidentally ingested her first dose of Fentora despite having received directions for buccal use. This patient's medication history included intervertebral disc protrusion, migraine, and sciatica. At the time of the report, the patient was still taking Fentora.

Comments: *Application site reactions are labeled for Fentora. In all three cases, the application site reactions appear to be related to the use of Fentora 1) given the site of the reactions (gum/tongue) where Fentora was applied, 2) the close temporal relationship between the events and the use of Fentora, and 3) the positive dechallenge in 2 of 3 cases. It is noteworthy that in the second case, the patient was instructed to use Fentora sublingually by the physician due to the bleeding of the gums, and in the last case, the patient accidentally ingested Fentora; in both cases, the wrong route of administration was applied despite knowing the proper directions for use.*

3.3.2.6 Suicidal Attempt/Completed Suicide (n=2)

There was one report each of suicidal attempt and completed suicide in this case series. The latter case of completed suicide was previously discussed in the *Death* section. One case of suspected suicidal attempt was reported involving a 49 year old male who intentionally ingested an undisclosed amount of Fentora and two other unspecified substances. The event resulted in no adverse effects. Additional information was not provided in the report.

Comments: *The case involving a suicidal attempt was reported by AAPCC (American Association of Poison Control Centers), and therefore contained limited information about the case. In both cases, Fentora was used as a means for self-harm; the cases contained no evidence to suggest that Fentora may cause an individual to attempt suicide.*

3.3.2.7 Cerebrovascular Accident (n=1)

One report of CVA was received from a registered nurse regarding a 58 year old female with a history of stroke, who initiated Fentora 400 mcg (date and indication unknown). The patient was subsequently hospitalized for stroke at the time of the report. According to the reporter, neither the underlying cause nor the severity of the stroke was known.

Comments: *CVA is not a labeled event for Fentora. In this particular case, since there was a lack of clinical details such as the total amount of Fentora administered, past medical history to explain the underlying cause of the stroke, onset of event, and other concomitant medication use, we could not establish a relationship between the use of Fentora and CVA.*

3.3.2.8 Retching (n=1)

One report of retching was received from a 43 year old male consumer, with a history of anxiety, who initiated Fentora 600 mcg BID for an unspecified chronic pain. His concomitant medications were Duragesic, Xanax, and possibly Actiq. After starting Fentora, the patient experienced a gag reflex due to the fizzing and the taste of Fentora. The patient spit the tablet out after 3 minutes, and the Fentora therapy was discontinued; the event resolved. The patient also mentioned that he had tried using Fentora under his tongue on an unknown date. No further information was available.

Comments: *In this case, the reported event appear related to the use of Fentora given the narrative descriptions and the dechallenge of the gag reflex. This is an expected event for Fentora. It is noteworthy, however, that this is one of 3 cases reporting sublingual use of Fentora in this case series.*

3.3.3 Review of Medication Error Cases

A total of 63 cases associated with the use of Fentora were retrieved on March 18, 2008, from the AERS database search, forty-three of which were medication errors. Twenty of the 63 reports did not involve a medication error and were excluded from our analysis. These cases involved intentional overdose, adverse events, or did not contain enough information to determine if a medication error occurred. Reports of medication error represent more than two-thirds (68%) of all adverse events reported in AERS for Fentora.

Thirty-five of 43 the reported medication errors occurred in patients being treated for an off label use, four occurred in patients being treated for the approved indication of use, and four were unspecified. Similar types of errors were reported for both the off-label and on-label uses and can be categorized into the following broader types of error:

- Wrong route of administration (n=10)
- Improper Patient Selection (n=9)
  - off label use (n=7)
  - not on concomitant around the clock opioid (n=2)
- Improper frequency of administration (n=9)
- mcg per mcg conversion between Actiq/Fentora (n=6)
- Improper dose prescribed when converting to Fentora from Actiq (n=4)
- Wrong Drug (n=2)
- Improper Technique (n=1)
- Accidental Exposure (n=1)
- Accidental Overdose (n=1)

In twenty-two (n=22) of the cases no adverse event was reported or no outcome was given. Of the remaining twenty-one cases (n=21) identified in AERS, two cases (n=2) resulted in death according to the detail contained in the case narratives. Both deaths occurred in patients taking Fentora for off-label uses (i.e. back pain and migraines). In six cases (n=6), the medication error was caught before the medication error reached the patient. Four cases (n=4) resulted in patients requiring evaluation by a healthcare provider either in the emergency room or by consultation over the telephone due to respiratory depression or lightheadedness. Three cases (n=3) resulted in application site ulceration bleeding. Two cases (n=2) resulted in a lack of effect when taking Fentora. Two cases (n=2) resulted in withdrawal. One case (n=1) resulted in constipation, urinary retention, inability to stay awake, and inability to eat and drink. One case (n=1) resulted in decreased blood sugar. Appendix 3 contains a summary of these cases. We noted, 22 errors were reported to the Agency following the publication of the Public Health Advisory, Health Care Provider Sheets and Dear Doctor/Dear Health Care Provider letters and these are highlighted in grey in the table.

Our analysis noted 81% of all errors reported occurred with an off-label use, 9% with on-label use, and the remaining cases occurred with an unspecified indication. The major categories of off- label use include chronic/non-cancer pain, back pain and migraines. Other reported off-label uses included neck pain, mandibular jaw pain, shoulder pain, reflex sympathetic dystrophy, Guillain Barre syndrome, pain resulting from an automobile accident, and pain from a gunshot wound. Twenty-two of the reported medication errors occurred following the dissemination of the Dear Doctor Letter, Dear Healthcare Professional Letter, Public Health Advisory, and Healthcare Information Sheet. Of the 22 errors occurring after the dissemination of the above safety information, all but one (95%) occurred in off-label uses.

Despite the large number of medication errors occurring in off label use, similar types of medication errors were reported for the approved use as well. We categorized these errors into the following types: wrong route of administration, improper patient selection, improper frequency of administration, mcg per mcg conversion between Actiq/Fentora, improper dose when converting to Fentora from Actiq, wrong drug, improper technique, accidental exposure, and accidental overdose. Medication errors associated with improper dosing were the most numerous, however, these cases were further broken down into the improper frequency of administration, mcg per mcg conversion between Actiq/Fentora, improper dose when converting to Fentora from Actiq categories. The large majority (88%) of the medication errors identified were in direct contradiction to the goals stated in the Sponsor's Risk Minimization Action Plan for the product.

3.3.3.1 Wrong Route of Administration

The majority of the cases describe Fentora being administered sublingually rather than the intended buccal route of administration. There are several factors that could lead to incorrect route of administration errors in association with Fentora. Fentora has been shown to cause application site ulceration, and as noted in the cases, some patients were using the sublingual route in an attempt to avoid such reactions. In addition to not fully understanding the appropriate route of administration and trying to avoid ulceration, the appearance of the tablet may have contributed to improper administration of the product. Although Fentora is a buccal tablet, its appearance is identical to an oral tablet, as such, there is nothing about the tablet appearance itself that would lead a patient to believe that the tablet should not be administered orally. We did note patients who swallowed the tablet whole. Although swallowing the tablet whole does not represent an increased risk for overdose, it may decrease the absorption. This decreased absorption may impact the perceived lack of effect some of these patients experienced. Current Fentora labeling and labels contain a warning against swallowing the tablets whole but there is no warning against sublingual administration. However, the Sponsor does present data supporting sublingual use in the Efficacy Supplement under review.

3.3.3.2 Improper Patient Selection

Our analysis identified two cases involving the use of Fentora in chronic pain patients that were not on concomitant around-the-clock opioid therapy. However, the majority of cases involving improper patient selection occurred with patients being treated for an off-label use. Since Actiq and Fentora have the same active ingredient, overlapping and achievable doses, and currently have the same indication (i.e. breakthrough cancer pain), practitioners may believe that Fentora can be used in a similar context as Actiq. Fentora labeling has been revised to strengthen the warning with regard to proper patient selection and its approved indication of use.

3.3.3.3 Improper Frequency

The majority of improper administration frequency cases describe Fentora as being administered with less than four hours between doses or more than four times daily. Other cases describe Fentora being prescribed on a regularly scheduled interval (e.g. twice daily), rather than as needed. Fentora labeling clearly states that only one additional dose may be taken if breakthrough pain is not relieved at least 30 minutes after taking the first dose, with a maximum of four breakthrough pain episodes treated daily. If the patient experiences more than four breakthrough pain episodes daily, it is recommended that the around-the-clock opioid therapy be adjusted to better address the patient's pain. The medication errors identified associated with improper dosing frequency involved prescriptions instructing the patient to take Fentora at dosing frequencies incongruent with the dosing instructions in the prescribing information. Some of these errors may have been a result of prescribers misinterpreting the directions for re-dosing within a single breakthrough pain episode 30 minutes after the first dose as instructions to allow

for repeating the dose every 30 minutes. However, it is apparent that all of the errors involving improper dosing frequency appear to be a result of knowledge deficit on the part of prescribers with regard to correct use of Fentora despite instructions regarding re-dosing and limiting the use of Fentora to four breakthrough pain episodes per day in the prescribing information. We note that the Dosage and Administration section and Precautions section, "Information for Patients and Their Caregivers" subsection of the prescribing information were revised February 7, 2008, to more clearly communicate the correct instructions for re-dosing within a single breakthrough pain episode.

3.3.3.4 mcg per mcg Conversion between Actiq/Fentora

Six medication error conversion cases describe prescribers converting patients from Actiq to Fentora on a microgram per microgram basis. Dosing-conversion instructions for Actiq to Fentora conversion are provided in the prescribing information, as the bioavailability differs between these two products. However, evidence demonstrates that many prescribers are unaware that these products are not interchangeable on a microgram per microgram basis. Prescribers may have assumed that conversion from Actiq to Fentora did not require special consideration due to the fact that Actiq and Fentora contain the same active ingredient (fentanyl) and have overlapping or achievable dosage strengths between the two products (i.e. 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg). These overlapping characteristics may contribute to the confusion, despite warnings in the prescribing information and on the carton labeling. We note the Dosage and Administration section of the prescribing information was revised February 7, 2008, to strengthen these differences in dosing.

3.3.3.5 Improper Dose When Converting To Fentora from Actiq

Four cases describe prescribers prescribing an improper dose when converting patients from Actiq to Fentora. We note that none of these cases involved microgram for microgram conversion, but rather conversion that is incongruent with the conversion instructions in the prescribing information. Since the available microgram strengths of Fentora are exactly one-half the microgram strengths of Actiq (100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg for Fentora vs. 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg for Actiq), prescribers may have assumed that conversion from Actiq to Fentora only required halving the patients Actiq dose to determine the Fentora dose. This may have contributed to the confusion despite warnings in the prescribing information and on the carton labeling. We note the Dosage and Administration section of the professional insert was revised February 7, 2008 to strengthen these differences in dosing.

3.3.3.6 Wrong Drug

In two cases, Fentora was substituted for Actiq at the pharmacy level and dispensed. This type of medication error is most likely attributed to knowledge deficit on the part of pharmacy personnel with regard to the fact that Fentora is not a generic equivalent to Actiq, and cannot be substituted for Actiq without dose conversions by the prescriber. Pharmacy personnel may have assumed that substitution of Fentora for Actiq was permitted due to the fact that Actiq and Fentora contain the same active ingredient (fentanyl) and have overlapping or achievable dosage strengths between the two products (i.e. 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg). The labeling has been revised and warns pharmacy personnel against substituting of Fentora and Actiq.

3.3.3.7 Improper Technique

We noted one case (n=1) in which a patient was prescribed to take one-half a 400 mcg tablet of Fentora twice daily. Causality for the error was not included in the medication error report. The error can most likely be attributed to a knowledge deficit on the part of the prescriber with regard

to the fact that Fentora tablets are not to be split, despite warnings in the Dosage and Administration section of the prescribing information. Often at the point of administration, only the blister label is available to the patient, and if the blister label does not contain a warning advising against tablet splitting, patients may not be aware that Fentora must not be split. We note the revised Fentora labeling approved February 7, 2008, did not include any additional warnings regarding tablet splitting.

3.3.3.8 Accidental Exposure

One case of accidental exposure was reported in which a patient removed the Fentora prior to administration and placed in an unmarked container and it was mistaken for aspirin and ingested by another family member. We note there are warnings on the blister label and in the Medication Guide advising against the removal of Fentora from the blister until ready for use.

3.3.3.9 Accidental Overdose

We noted one case (*n=1*) of accidental overdose associated with the use of Fentora that resulted in the patient's death. Causality behind the accidental overdose was not included in the medication error report, and thus it is not possible to determine what caused the overdose and resultant death

3.4 SUMMARY OF RISKMAP REPORTS

3.4.1 Drug Use

RiskMAP Reports of Fentora off-label use using both syndicated third-party national audit data and information provided to Cephalon Medical Services department show that off-label product use has ranged from approximately 83% t0 86% of total product use since product approval.

RiskMAP Reports of Fentora opioid naïve use[22] show use of Fentora in opioid naïve patients increasing from 14.2% initially (reported in the 1st Quarterly RiskMAP Report), to 24.1% (reported in the 4th Quarterly RiskMAP Report), since product approval.

3.4.2 Signals of Misuse, Abuse, or Diversion

The 4th Quarter Fentora RiskMAP Report presents concerning rates of unique recipients of dispensed drug (URDD) in several 3-digit zip codes located around the U.S. for the following RADARS® system studies: Drug Diversion, Key Informant, Poison center, and Methadone Treatment Program.[23] These studies/signal detection programs monitor for prescription drug abuse, misuse, and/or diversion.

4 DISCUSSION

A RiskMAP was approved at the time of the initial FDA approval of Fentora as an important part of its postmarketing risk management to, 1) minimize the use of Fentora by opioid non-tolerant individuals, minimize misuse of Fentora, and minimize unintended (accidental) exposure to Fentora. The RiskMAP consisted primarily of healthcare provider and patient education on about the risks and benefits of Fentora, a reporting and data collection system for safety surveillance, and a plan to monitor, evaluate, and determine the incidence of use of Fentora by opioid non-tolerant individuals, misuse of Fentora, and unintended (accidental) exposure to Fentora. Fentora also has state and federal restrictions on manufacturing, distribution, prescribing,

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[22] Fentora RiskMAP Quarterly Reports (1 to 4), IMS longitudinal patient data

[23] Fentora RiskMAP 4th Quarterly Report submitted February 26, 2008

dispensing, storage, and disposal on the basis of its Schedule II status under the Controlled Substance Act.

- *Drug Utilization*

  Fentora use has increased more than five-fold since the initial 1st quarter launch in September 2006, with most use occurring off-label in non-cancer pain indications. A 2007 review of concurrency data of Fentora with other marketed pain medications suggests that use in opioid non-tolerant individuals is not uncommon with Fentora. In year 2007, approximately 59% of patients who filled a prescription for Fentora also filled a prescription from the pain market.[24]

  Fentora® was the fourth most commonly dispensed fentanyl product from U.S. retail pharmacies in year 2007 according to Verispan's Vector One®: National data. The number of prescriptions dispensed for Fentora® between years 2006 and 2007 increased by approximately 521% from approximately 14.6 thousand prescriptions in year 2006 to 91 thousand prescriptions dispensed in year 2007. The majority (approximately 68%) of prescriptions dispensed in outpatient retail pharmacies for Fentora® are for patients aged 41-65 years old. Patients aged 26-40 years old followed with approximately 23% of dispensed prescriptions for Fentora® for years 2006-2007. Prescriptions for Fentora® dispensed to pediatric patients age 0-16 years old comprised less than 1% of all Fentora® prescriptions dispensed in years 2006-2007. Trends for patient data are similar to that of prescription data.

- *Adverse Event Cases*

  The AERS review of 19 Fentora cases did not reveal any notable unexpected safety concerns. Most of the reported adverse events were mentioned in only one report except for medication errors (10)[25], lack of efficacy (6), somnolence (3), application site bleeding (2), intentional overdose (2), overdose (2), accidental overdose (2), intentional drug misuse (2), and loss of consciousness (2). Most of these events are labeled for Fentora. Notable unlabeled events included acute myocardial infarction, cerebrovascular accident, dysarthria, and dysuria; in these cases, there was insufficient clinical evidence to conclude that Fentora was directly or solely related to the reported events. Fentora was most commonly used for non-cancer pain; Fentora was used for an approved indication (cancer pain) in only 1 case.

  It is noteworthy that 53% of the adverse event reports cited medication errors involving prescribing errors, pharmacy dispensing errors, and incorrect route/frequency of drug administration by patients. From a safety perspective, it is concerning that there were cases of incorrect conversion from Actiq to Fentora or that Fentora was considered a generic version of Actiq; Fentora is not bioequivalent to Actiq on a mcg to mcg basis. In patients who are not opioid tolerant, these types of medication errors could have a serious outcome. It is also concerning that the wrong routes of administration (e.g. sublingual) were used by patients despite knowing the proper directions for use.

  Thirty-two percent of the cases reported overdoses (with equal numbers of intentional and accidental overdoses) and 11% reported intentional misuses. In the accidental overdose and exposure cases, it is possible that the events could have been prevented if there was no

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[24] Worthy K, Governale L, Division of Epidemiology, Concurrency Analysis VOCON: Fentora or Actiq with Pain Market Products, April 1, 2008

[25] *See **Medication Error Analysis** section of this review for a complete analysis of all medications errors, including potential/actual errors that did not lead to an adverse event (n=16; excluded from AE analysis) and medication errors associated with an adverse event (n=10).* The AERS Database was searched for all AEs on February 28, 2008 and for Medication Errors on March 18, 2008.

pharmacy error or if the Fentora tablets were better stored in the home. The intentional overdoses and drug misuse cases showed that drug diversion is occurring despite a RiskMAP for Fentora to minimize these events. One case of overdose illustrated the importance of proper patient selection, requiring sufficient around-the-clock opioid use prior to Fentora.

Five deaths were reported in this case series, and the causes of death were accidental fentanyl overdose (2), underlying metastatic leiomyosarcoma (1), suicide (1), and unknown (1). Three of 5 deaths (accidental OD-2, suicide-1) were related to the use of Fentora; in the 2 accidental overdose cases, the safety concern is that a medication error occurred at the pharmacy level, even though this product has a RiskMAP with an educational component for pharmacists to prevent such errors. The safety concern regarding the suicide case is that a large number of Fentora tablets was readily available for this patient; although it is impossible to prevent suicide from occurring, this case illustrated that despite the efforts to reduce drug diversion through a RiskMAP for this product, it is still possible to access this drug for self-harm.

- *Medication Error Cases*

  The potential for medications errors was recognized prior to approval and risk minimization strategies were implemented as part of the RiskMAP to address this potential. Despite these strategies, medication errors associated with the use of Fentora occurred soon after marketing. Additional strategies were subsequently implemented including distribution of Dear Doctor and Dear Healthcare Professional Letters and to revisions to the labeling to better communicate these risks. The Agency also published its own Public Health Advisory and Healthcare Information Sheet. Despite all of these activities, medication errors continue to occur and in fact more than half (51%) of the medication errors were reported after dissemination of the Dear Doctor Letter, Dear Healthcare Professional Letter, Public Health Advisory, and Healthcare Information Sheet.

  Improper use and medication errors account for more than two-thirds of the adverse events reported with Fentora. The majority of these adverse events occurred when patients were being treated for off-label uses for Fentora, such as back pain, chronic/non-cancer pain, and migraines. Medication errors include conversion errors between Actiq and Fentora, improper frequency of administration, wrong route of administration, wrong drug dispensed, improper administration technique, accidental exposure, and accidental overdose.

Based on our review of the postmarketing experience with Fentora, we do not believe the RiskMAP has been effective in minimizing the risks it was developed and implemented to minimize. Fentora RiskMAP Reports and our own drug utilization data reviews demonstrate data that is trending opposite of what would be expected with effective risk minimization strategies. Off-label use rather than indicated use dominates for the product; use in opioid intolerant patients has been steadily increasing; and signals of product misuse, abuse, and diversion are appearing. In addition, medication errors related to dosing and administration dominate the adverse event reports for Fentora.

Cephalon has not proactively considered or instituted interventions and/or adjustments to address the RiskMAP goal failures, in particular RiskMAP Goal # 1 (Fentora should be used only by opioid tolerant patients with cancer). Instead, Cephalon uses the large extent of product off-label use (a goal failure under the RiskMAP), to justify the proposed expanded indication for Fentora. Expanding the Fentora indication as proposed will most likely amplify and exacerbate the adverse event trends and use patterns (including use in opioid non-tolerant individuals) we have already observed.

There are different risk mitigation strategies for products ranging from routine measures such as increasing the prominence of safety information in product labeling or limiting the product's indication to a targeted education/communication and/or outreach strategies, to a program with restrictions on prescribing, distribution, dispensing, and/or administration as elements to ensure safe use of the drug product. These more restrictive risk management programs are usually reserved for those products that that have clinically important safety concerns that cannot be managed by routine risk management tools.

5 CONCLUSION

OSE does not believe the strategies developed and implemented under the Fentora RiskMAP have been effective in minimizing the potential risks associated with the product.

Expanding the Fentora indication as proposed to include treatment of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying chronic pain will most likely amplify and exacerbate the postmarketing trending we have seen regarding opioid naïve use, all medication errors, and abuse, diversion, and misuse because of increased use. Additional and /or stricter risk minimization strategies to ensure the safe and appropriate use of Fentora should be implemented and evaluated for effectiveness with the current limited indication where the benefits outweigh the risks before expanding use to a broader population.

6 RECOMMENDATIONS

We recommend The ALSDAC and DSARM Committee members discuss the following issues:

- Whether the indication should be broadened in light of the safety issues identified with the more limited indication;
- Should stricter risk mitigation strategies be developed to further minimize the potential for abuse, diversion, misuse and inappropriate use in the opioid non-tolerant patients;
- Whether additional strategies are need to prevent medication errors.

APPENDICES

APPENDIX 1: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients. Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

APPENDIX 2: TABLES AND FIGURES

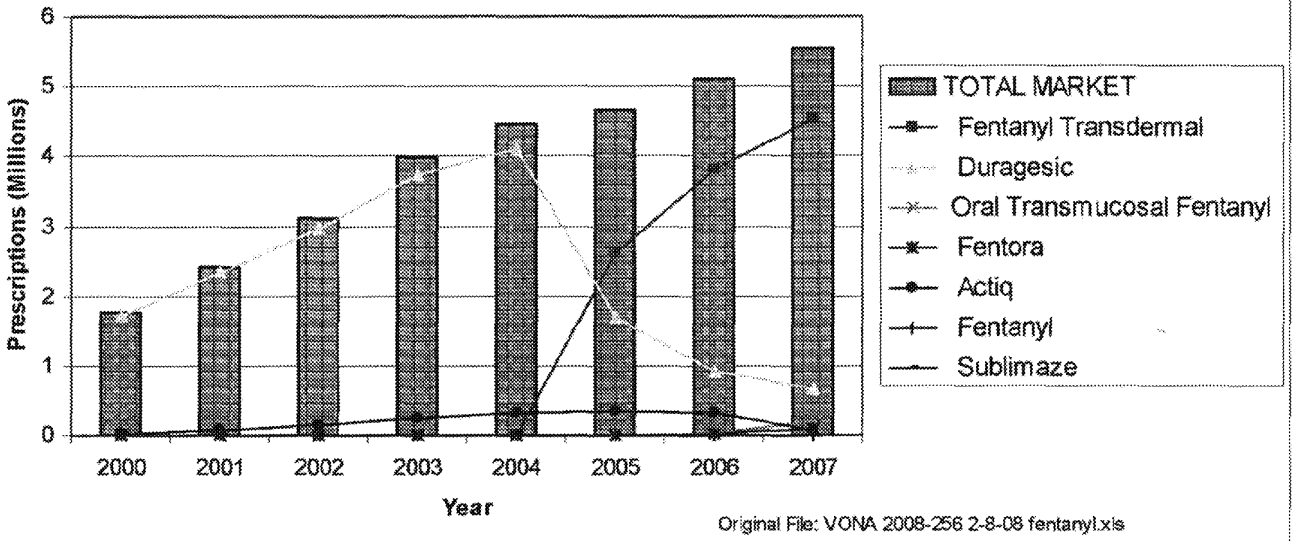
Table 1: Projected Number of Prescriptions for Fentanyl Products Dispensed from U.S. Retail Pharmacies , 2000-2007

	2000		2001		2002		2003		2004		2005		2006		2007	
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %
TOTAL MARKET	1,759,668	100.0%	2,405,321	100.0%	3,122,259	100.0%	3,980,412	100.0%	4,444,616	100.0%	4,658,670	100.0%	5,099,351	100.0%	5,545,675	100.0%
Fentanyl Transdermal	--	--	--	--	--	--	--	--	--	--	2,605,608	55.9%	3,818,097	74.9%	4,524,034	81.6%
Duragesic	1,729,950	98.3%	2,334,775	97.1%	2,965,312	95.0%	3,723,901	93.6%	4,113,873	92.6%	1,689,542	36.3%	916,516	18.0%	671,472	12.1%
Fentanyl Oral Citra	--	--	--	--	--	--	--	--	--	--	--	--	31,321	0.6%	187,986	3.4%
Fentora	--	--	--	--	--	--	--	--	--	--	--	--	14,620	0.3%	90,751	1.6%
Actiq	22,601	1.3%	63,884	2.7%	151,487	4.9%	249,531	6.3%	324,295	7.3%	356,815	7.7%	313,166	6.1%	65,931	1.2%
Fentanyl	6,083	0.3%	5,847	0.2%	5,014	0.2%	6,856	0.2%	6,375	0.1%	6,667	0.1%	5,608	0.1%	5,448	0.1%
Sublimaze	728	0.0%	689	0.0%	385	0.0%	95	0.0%	70	0.0%	38	0.0%	23	0.0%	50	0.0%
Fentanyl Oralet	306	0.0%	126	0.0%	61	0.0%	29	0.0%	3	0.0%	--	--	--	--	3	0.0%

Verispan LLC, Verispan Vector One®: National, 2000-2007, extracted Feb 08. File: VONA 2008-256 2-8-08 fentanyl.xls

Figure 1: Total Dispensed Prescriptions for Fentanyl Products from U.S. Retail Pharmacies, 2000-2007

Verispan Vector One®: National (VONA). Extracted 2/2008



Original File: VONA 2008-256 2-8-08 fentanyl.xls

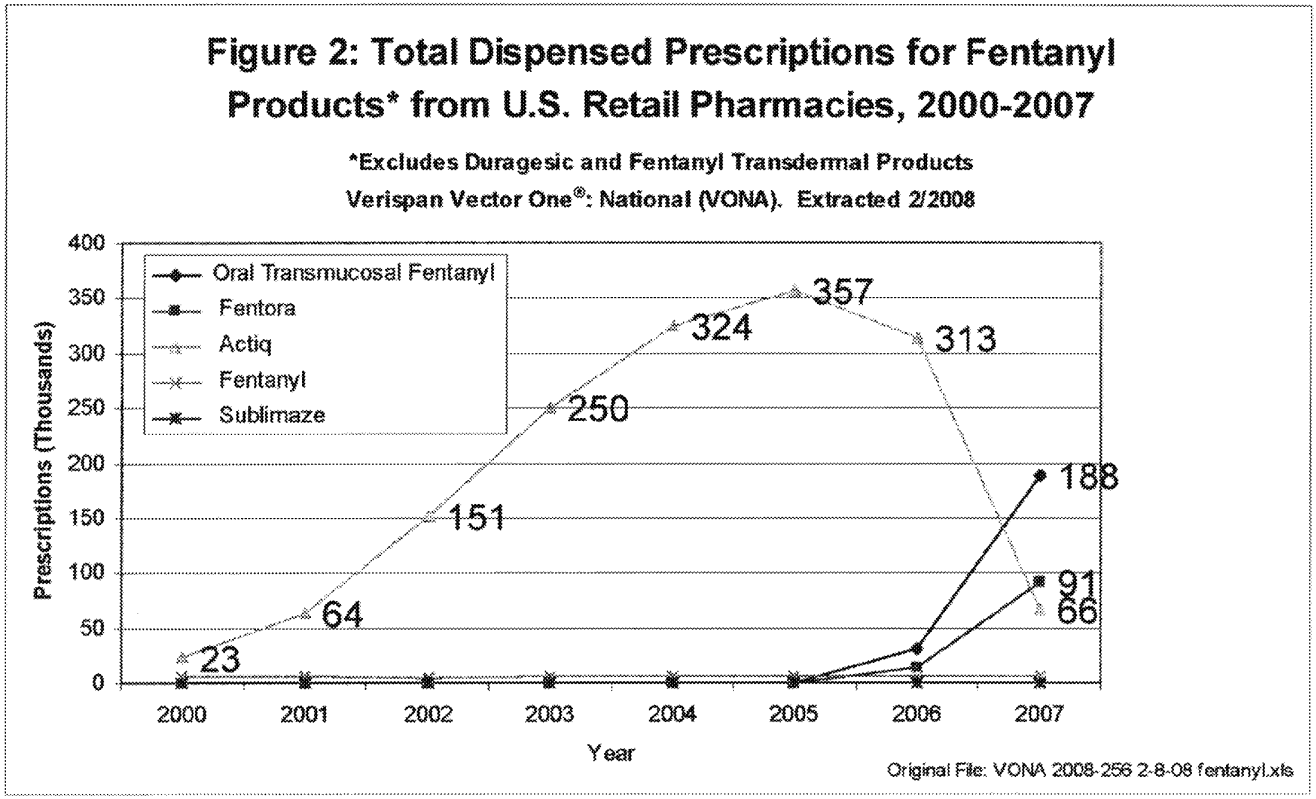


Table 2: Projected Number of Fentora® Prescriptions Dispensed, by Age, to U.S. Retail Pharmacies , 2006-2007

	2006 Retail TRxs	Share %	2007 Retail TRxs	Share %
Fentora®	14,614	100.0%	90,815	100.0%
0-2	4	0.0%	31	0.0%
6-11	3	0.0%	1	0.0%
12-16	5	0.0%	93	0.1%
17-25	236	1.6%	1,553	1.7%
26-40	3,295	22.5%	21,263	23.4%
41-65	10,074	68.8%	61,814	68.1%
66+	1,006	6.9%	5,942	6.5%
UNSPEC.	11	0.1%	118	0.1%

Verispan LLC, Verispan Vector One®: National, 2006-2007, extracted March 08. File: VONA 2008-226 3-11-08 fentora actiq age.xls

Table 3: Total number of patients*, by age, receiving a prescription for Fentora® from outpatient retail pharmacies, 2006-2007

	2006		2007	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
Fentora®	**8,703**	**100.00%**	**23,035**	**100.00%**
0 - 2	2	0.03%	24	0.10%
6 - 11	3	0.03%	1	0.01%
12 - 16	4	0.05%	18	0.08%
17 - 25	146	1.68%	486	2.11%
26 - 40	1,820	20.91%	4,898	21.26%
41 - 65	6,030	69.28%	15,303	66.43%
66 - 85	684	7.86%	2,437	10.58%
Unknown age	25	0.28%	96	0.42%

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.
Source: Verispan, LLC: Total Patient Tracker, January 2006 - December 2007, Extracted Feb 2008.
File: TPT 2008-226 2-21-08 Fentora Age.xls

APPENDIX 3: AERS MEDICATION ERROR CASES

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5525091-6 11/20/2007	Accidental overdose	Back pain		400 mcg, every 8 hours		Death	A physician report received, via a sales representative, regarding a 40-year-old female who initiated Fentora (fentanyl buccal tablet), 400 mcg every eight hours, on [redacted] for the treatment of breakthrough chronic back pain related to radiculopathy. Prior to initiating Fentora, the patient was receiving pain therapy with Duragesic (fentanyl transdermal patch), 50 mcg/hour, one to two patches every 72 hours for one year. After Fentora was initiated the Duragesic dose was initially reduced to 25 mcg/hr and then was increased back up to 50 mcg/hr. The patient was not taking any other concomitant medications. The patient informed the physician of her plans to travel out of town during an office visit on [redacted]. At that time, the physician wrote another prescription for Fentora but with instructions to the pharmacy no to fill until [redacted]. The physician learned through n obituary posted in the local newspaper that the patient had died on [redacted]7. The coroner subsequently contacted the physician and reported that the cause of death was due to an accidental overdose and confirmed that the patient had died during her travel out of town. Thereafter, the physician contacted the pharmacy and discovered that the last prescription was dispensed on [redacted] and not [redacted] as instructed. ...The autopsy report determined that the cause of death was due to accidental acute fentanyl toxicity with coronary atherosclerotic disease as a contributory factor.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5644155-X 2/28/2008	conversion	Automobile Accident	Actiq 400 mcg to Fentora 200 mcg	200 mcg every six hours		Decreased blood sugar	...A consumer report was received regarding an 82-year-old male who initiated Fentora (fentanyl buccal tablet) 200 mcg buccally since [redacted] every six hours as needed for the treatment of status post an automobile accident. The patient was switched from therapy with Actiq (oral transmucosal fentanyl citrate) 400 mcg due to dental problems and increased blood sugar levels. Concomitant opioid medication included extended-release morphine. Concurrent medical history included diabetes. Six days after initiating Fentora on [redacted] the patient experienced shaking and was unable to sleep. It was noted that since beginning therapy with Fentora, the patient's blood sugar had been ranging between 101 to 104 in the morning from his usual 150. On [redacted] due to persistent symptom, the patient discontinued Fentora and reinitiated Actiq. The symptoms resolved on [redacted]
5616382-9 2/4/2008	conversion	Neuropathy	Actiq 800 mcg to Fentora 600 mcg	600 mcg three to four times daily		Application site ulcers and burning	...This 54-year-old male, initiated Fentora therapy for the treatment of autoimmune neuropathy. The patient was initially taking Actiq (oral transmucosal fentanyl citrate) at dose of 800 mcg, two to three times daily; however, after experiencing dental caries and gum problems, pain therapy was switched to Fentora therapy in Jul-07 at dose of 600 mcg three to four times daily, which has a higher bioequivalency on a mcg per mcg basis compared to Actiq. Since Fentora was initiated, the patient experienced application site ulcers and burning on the buccal mucosa whenever he used Fentora. Therapy was discontinued in Jan-08 and the events subsided. The physician (patient) considered the events to be possibly related to Fentora.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5644154-8 2/28/2008	conversion	reflex sympathetic dystrophy	Actiq 600 mcg to Fentora 400 mcg			Prescription was not filled at time of report	...A consumer report received regarding an adult female who received a prescription for Fentora (fentanyl buccal tablet) 400 mcg after being switched from therapy with Actiq (oral transmucosal fentanyl citrate) 600 mcg for the treatment of reflex sympathetic dystrophy. The prescription was not filled at the time of the report.
5341436-4 6/1/2007	Improper Frequency	chronic non-cancer pain		1 every 2 to 4 hours as needed		No adverse event reported	...A 45-year-old male from the United States...medical history included Chron's disease...multiple kidney stones...Concomitant medications included escitalopram, esomeprazole, ramipril, fentrinol for pain, oxymorphone, and consotuss...
5379966-1 7/6/2007	Improper Frequency	chronic non-cancer pain		1 or 2 tablets as needed daily		No adverse event reported	This spontaneous report from a patient concerns a 51 year old female from the United States: SDZ0099290. The patient's medical history and concurrent conditions included: non-drinker, non-smoker, nerve damage to the back in 1990, breakthrough pain, and anxiety. ...Concomitant medications included lorazepam for anxiety, clopidogrel sulfate for blood thinner, and fentrinol for breakthrough pain.
5413445-8 8/10/2007	Improper Frequency	chronic non-cancer pain		400 mcg, 2 to 3 times daily		No adverse event reported	...taking Avinza 120 mcg/1 daily; Fentora 400 mcg/ 2 to 3 times per day as needed; Zanaflex as need; Ibuprofen 800 mg/3 times daily...Generally in good health other than osteo-arthritis, disc disease, carpal tunnel syndrome, and migraine. Under supervised Pain Management...

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5486403-5 10/15/2007	Improper Frequency	Bone pain		100 mcg every hour		No outcome reported	...A report received from the mother of 16-year-old male who reported that her son had been taking Actiq (oral transmucosal fentanyl citrate), 200 mcg alternating with 400 mcg up to six times daily beginning in 2005, and was recently switched to Fentora (fentanyl buccal tablet) therapy in Aug-07, 100 mcg, for the treatment of bone pain. Concomitant medication included fentanyl transdermal patch 250 mcg/hr every three days, Fosamax (alendronate sodium), 70 mg weekly, and Celebrex (celecoxib), 100 mg three times daily. The mother reported that Fentora only provided her son with "short term relief." To obtain pain relief, her son needed to take Fentora every hour. The physician had since written a prescription for 200 mcg strength tablets.
5633671-2 2/20/2008	Improper Frequency	Migraines		As needed		No adverse event reported	...The purpose of the patient's call was to learn about the maximum dose of Fentora she could take. The patient indicated that her physician told her to take it as needed and the prescription label read to take as needed. Neither the dose frequency nor the maximum amount per day was written on the prescription. The physician gave her an information pamphlet and instructed her to discuss her concerns about the dose with her pharmacist. At this time, the patient is taking approximately three doses of Fentora per day.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5452217-5 9/13/2007	Improper Frequency	Migraines		400 mcg every 30 minutes		Death	On an unknown date in May-07, the patient was switched from Actiq to Fentora 400 mcg and the physician instructed her to use only one tablet. The physician wrote instructions on the prescription that the dose could be repeated once if no pain relief was obtained after 30 minutes. The physician was told by the patient's husband that he thought the dispensed instructions stated that Fentora could be taken every 30 minutes but the physician could not verify if true...
5376699-2 7/1/2007	Improper Patient Selection	Back pain				No adverse event reported	A consumer report received regarding a 46-year-old male, with a history of epilepsy since childhood, who initiated Actiq (oral transmucosal fentanyl citrate) therapy 600ug four times daily as needed, in 2001, for the treatment of back pain. In Nov-06, therapy was switched to Fentora (fentanyl buccal tablet) due to insurance purposes. Then in Jan-07, therapy was switched back to Actiq also due to insurance purposes. Actiq continued until [redacted] when therapy was abruptly stopped as the patient was no longer able to afford it...
5354381-5 6/12/2007	Improper Patient Selection	chronic non-cancer pain				No adverse event reported	This spontaneous report from a physician concerns a 69 year old female from the United States: 1-426086224. The patient's medical history and concurrent conditions included: DDD, spinal pain, and arthritis (entire body e.g. thumbs, pelvis legs)...Concomitant medications included fentanyl citrate, cetirizine hydrochloride, SSRI, tramadol hydrochloride, and fentora.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5565961-6 12/19/2007	Improper Patient Selection	chronic non-cancer pain				No adverse event reported	...The patient's medical history and concurrent conditions included: cord decompression surgery in 2000, exploration of sciatic nerve in 2002, herniated disc in 1999, left hip replacement, shoulder compression (right and left shoulder), chronic pain, nerve pain, a smoker (social), total hip resurface, and vascular necrosis (multiple joints). The patient's weight was 210 pounds. The patient was treated with fentanyl-TTS (reservoir patch, transdermal, batch 0633870, expiry DEC-2007), 100ug/hr initiated in 2003 for chronic pain...Concomitant medications included meloxicam for chronic pain, fentrinol for chronic pain, vicodin for chronic pain, and antidepressants for nerve pain... The reporting physician stated the patient experienced "no adverse response".
5629024-3 2/15/2008	Improper Patient Selection	Neck pain				Lack of effect	30-Jan-08: A report was received from a consumer regarding an adult male who initiated Fentora (fentanyl buccal tablet) therapy, 100ug, on an unknown date, for the treatment of neck pain. Concomitant medication included Duragesic (fentanyl transdermal patch) 75ug/hr. The patient reported that the 100ug dose "was like taking an aspirin for a migraine" and it did not help his pain. The dose was increased to 200ug, but the patient reported that the dose did not work either. The patient has been taking two 200ug to achieve pain relief. According to the patient, his physician plans to increase his dose to 400ug.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5376700-6 7/1/2007	Improper Patient Selection	Shoulder pain				Withdrawal	A consumer report received regarding a 43-year-old male who initiated Actiq (oral trasmucosal fentanyl citrate) therapy 1200 mcg six times daily, on an unknown date, for the treatment of chronic shoulder pain. The patient had been taking Actiq for several years, but was forced to discontinue therapy in 2006 due to cost and workman's compensation...Withdrawal symptoms occurred after the patient was switched from Actiq 1200 mcg to Fentora 400 mcg. In Dec-06, Fentora was discontinued and Actiq 1200 mcg was restarted...
5610445-X 1/30/2008	Improper Patient Selection	Migraines				No adverse events/ Pt died due to unrelated causes	...This adult female (age not reported) had been initially treated with Actiq (oral transmucosal fentanyl citrate) for migraines for many years until Apr-07 when her insurance carrier denied coverage. Therapy was subsequently switched to Fentora and therapy continued since that time. The patient was prescribed one box per month; however, the Fentora dose, strength, and frequency were unspecified. The patient was prescribed other medications, however, it was not known if the patient was taking other opioids...The patient died on [redacted]...a fentanyl overdose was excluded as a [redacted] ause of death.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5510585-X 11/8/2007	Improper Patient Selection No around-the-clock opioid therapy	chronic non-cancer pain				Respiratory depression, hospital admission	...A physician report received, via a sales representative, regarding a female (age unknown) who initiated Fentora (fentanyl buccal tablet, dosage not specified) for the treatment of non-cancer pain in approximately Apr-07. They physician specified that the patient was opioid tolerant; however, specific concomitant medications were not reported at this time. On an unspecified date, the patient had taken one dose of Fentora. No other medications were taken that day. Sometime thereafter, the patient was driving and just before reaching the driveway to her home, she passed out. The patient's skin was observed to be blue by the roommate. The patient was transported to the hospital via the paramedics...Although the patient is described by the physician as being 'opioid tolerant', the physician's review of this office notes indicated that this patient may not have been taking 'around-the-clock' opioid medication as prescribed...It has been confirmed that the patient was not taking around-the-clock (ATC) opioid medication.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5254744-2 3/1/2007	Improper Patient Selection	Back pain		800 mcg daily		Withdrawal	...41-year-old male, who initiated Fentora (fentanyl buccal tablet) 800mcg daily, for the treatment of chronic lower back pain and failed surgery. On [redacted] the patient experienced delirium and presented to the emergency room. The patient was treated with Narcan (naloxone hydrochloride) and subsequently experienced a "violent withdrawal" which was treated with Demerol (meperidine HCl) It was concluded following unspecified results from a toxicology screen that the patient experienced serotonin syndrome. The event resolved. According to the physician, the event was considered to be due in part to the use of both Fentora and Cymbalta (duloxetine HCl). No further information was provided...
5484479-2 10/11/2007	Inappropriate Technique (tablet cutting)	chronic non-cancer pain		400 mcg, one-half tablet twice daily		No outcome reported	...A report received from a pharmacist regarding a written prescription for Fentora (fentanyl buccal tablet). The physician wrote a prescription for Fentora, 400 mcg, 'one half tablet' twice daily for the treatment of chronic non-cancer pain. Per the pharmacist, the patient was also receiving receiving methadone, 20 mg, three times daily. No patient information was provided, and it was not know if this prescription was new for the patient. The pharmacist called because he questioned whether the tablet could be split in half. No further information provided.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5336616-8 5/25/2007	mcg for mcg	Back pain	400 mcg Actiq to 400 mcg Fentora			Error caught by nurse before administration & changed to correct dose	A report received from a female consumer who was prescribed Fentora (fentanyl buccal tablet) for lower back pain. The patient was converted from 400 mcg Actiq (oral transmucosal fentanyl citrate) to 400 mcg Fentora therapy on an unspecified date. The nurse then informed the physician that the Fentora conversion chart recommends to start patients at 100 mcg if being switched from 400 mcg Actiq. The prescription was subsequently changed to Fentora 100 mcg without incident.
5142088-9 10/30/2006	mcg for mcg	chronic non-cancer pain	1600 mcg Actiq to 1600 mg Fentora 1600 mcg Actiq to 800 mcg Fentora			Error detected prior to filling	...A report received from a female patient regarding a prescribing error with Fentora (fentanyl buccal tablet). The patient had previously taken Actiq (oral transmucosal fentanyl citrate) 1600 mcg for the treatment of chronic non-cancer pain. The patient's pain management therapy was switched from Actiq to Fentora which as a greater bioavailability on mcg-per-mcg basis. The patient reported that her physician wrote a prescription for 1600 mcg instead of 800 mcg but she had not filled the Fentora 1600 mcg prescription prior to detecting the error. The patient subsequently spoke with her physician who concurred and planned to rewrite the Fentora prescription for 800 mcg.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5616381-7 2/4/2008	mcg for mcg	Gunshot wound	Actiq 800 mg to Fentora 800 mcg	800 mcg up to six times daily		No adverse events	...A report received from a registered nurse regarding a male patient who was prescribed Fentora (fentanyl buccal tablet) 800 mcg up to six times daily for the treatment of breakthrough pain secondary to a gun shot wound. Concomitant medications included hydormorphone 8 mg every three hours and Duragesic (fentanyl patches) 200 mcg per hour. The patient was no longer experiencing effective pain control with 800 mcg Actiq (oral transmucosal fentanyl citrate) and on [redacted] the patient was prescribed Fentora 800 mcg which has a higher bioavailability on a mcg per mcg basis compared to Actiq. The nurse indicated that the physician had discussed the conversion process at length with the company representative and had received educational materials as well, however, the physician assessed the patient's need for better pain control and felt that the Fentora dose was appropriate for this patient. The patient experienced no untoward effects and has been maintained on this dose for over one year with a good clinical effect.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5571008-8 12/20/2007	mcg for mcg	Pain related to brain condition	Actiq 600 mcg to Fentora 800 mcg			No adverse effects/ lack of effect	A report received from the mother of an 18-year-old male who initiated Fentora (fentanyl buccal tablet) therapy at 800 mcg, for the treatment of pain related to a rare brain condition (unspecified). Concomitant therapy included Avinza. The patient initially received treatment with Actiq (oral transmucosal fentanyl citrate) 800 mcg but it was discontinued due to dental issues. On an unspecified date, the patient was switched from Actiq 800 mcg to Fentora (fentanyl buccal tablet) therapy at 800 mcg, which has a greater bioavailability. The patient did not experience any untoward effects. Furthermore, the patient did not achieve the same clinical pain relief as compared to Actiq. Fentora was subsequently discontinued and Actiq was re-initiated...
5574462-0 12/26/2007	mcg for mcg		Actiq 600 mcg to Fentora 600 mcg			Application site burning and bleeding.	...Initially the patient was receiving therapy with Actiq (oral transmucosal fentanyl citrate) 600 mcg and in Jul-07, was switched to Fentora at the same dose, which is not bioequivalent on a mcg per mcg basis. The patient continued Fentora therapy for approximately eight days but discontinued it after experiencing application site burning and bleeding. Additionally, he stated that the taste was horrible and it did not help his pain. The patient was subsequently switched back to Actiq therapy on an unspecified dated. The application site events resolved approximately two days later.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5387156-1 7/11/2007	Wrong Drug "Generic" switch	Back pain	"Generic Switch" @ pharmacy			Lightheaded ness	...A consumer report received regarding a 44-year-old female who had been taking Actiq (oral transmucosal fentanyl citrate), 600 mcg lozenges since 2005, for the treatment of chronic back pain and was accidentally dispensed Fentora (fentanyl buccal tablet) 600 mcg on [redacted]. The patient reported that a prescription for Actiq was dropped off to her pharmacy on [redacted] and was placed on hold until approximately three weeks later when she called the pharmacy to have it filled. On [redacted], the prescription was picked up and on the prescription bag there was a note indicating that the contents included 17 brand Actiq and 13 generic OTFC. The generic substitute was actually Fentora (fentanyl buccal tablet) 600 mcg tablets. *Just after midnight on* [redacted] *the patient* took a Fentora tablet and experienced lightheadedness. The patient was concerned as she normally does not use an entire 600 mcg Actiq lozenge and when the entire 600 mcg Fentora tablet dissolved quickly, she called the local emergency room who then referred her to call the poison control center...The patient then contacted Cephalon after on [redacted] to learn more about Fentora and to understand if Fentora was a generic substitute for Actiq. The patient stated that her mother picked up the prescription for her and the pharmacy did not mention how the Actiq was substituted with another brand nor did the pharmacy contact her about it... Additionally, the Fentora tablets were placed in the Actiq box along with the Actiq lozenges with a note that "generic" were included. The lightheadedness subsided approximately 20 minutes later...

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5286022-X 3/30/2007	Wrong Drug (Insurance Prompt)	Back pain	"Generic Switch" @ pharmacy			Wrong drug not taken	...The patient was prescribed Actiq (oral transmucosal fentanyl citrate) 400 mcg, for the treatment of back pain. On [redacted], a new Actiq prescription was filled and dispensed to the consumer; however, when the consumer opened the carton, he saw 400 mcg Fentora tablets in lieu of Actiq. The consumer noted a section on the Fentora carton designated "for the pharmacist" that stated do not substitute and a call was placed to the pharmacist as the consumer was certain that the prescription was written for Actiq and not Fentora. The pharmacist informed the consumer that the insurance carrier would not cover Actiq and suggested Fentora as an alternative. When asked, the pharmacist admitted that he did not see the checklist on the Fentora carton and did not consult with the doctor before dispensing it. The consumer did not open the box of Fentora and was returned to the pharmacy where generic brand of oral transmucosal fentanyl citrate was subsequently dispensed...

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5371535-2 6/26/2007	Accidental Exposure	Back pain				Flushing, sweating, treatment at ER	...A consumer report received regarding a 73-year-old female, with a history of Alzheimer's disease, who experienced an accidental exposure to Fentora (fentanyl buccal tablet). The reported had been taking two Fentora strengths 600 mcg and 800 mcg, for back pain. The reporter indicated that on an unspecified date in Dec-06, two Fentora tablets were removed from their original packaging and placed into an unlabeled container. The reporter's mother had mistaken the tablets for aspirin and ingested both Fentora tablets. Immediately after ingestion, she experienced flushing and sweating. The paramedics were called and upon arrival, they discovered six Lidoderm patches on her skin. She was transported to the emergency room where she was treated with intravenous fluids for symptoms presumed to be due to lidocaine overdose; however, the emergency room physician was unaware that she had accidentally ingested Fentora. Nonetheless, she responded quickly to treatment and was subsequently released to home approximately one hour later.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5410296-5 8/9/2007	Wrong route	chronic non-cancer pain		200 mcg every eight hours	Oral	No adverse effects	...A consumer report received regarding a 45-year-old female who initiated Fentora (fentanyl buccal tablet) therapy, 200 mcg on [redacted] for the treatment of chronic pain. The patient accidentally ingested her first dose instead of "sucking on the tablet" as directed. Approximately three hours later, the patient had no ill effects...Follow-up conducted with the patient who indicated that she had been instructed on the proper use of the Fentora tablet and places it between the gum and cheek until dissolved. She also rotates the site with each use. The consumer reported that over the past two days, her gums have become bruised further described as red and tender...Follow-up information received from the consumer indicated that she had been taking Fentora at a dose of 200 mcg every eight hours and the event of bruising gums was resolving.
5500222-2 10/25/2007	Wrong route	chronic non-cancer pain		600 mcg twice daily	Sublingual	No adverse effect reported	A consumer report received regarding a 43-year-old male who initiated Fentora (fentanyl buccal tablet) therapy, 600 mcg twice daily, on [redacted] for the treatment of chronic pain. Later that day, the patient experienced his gag-reflex "overreacting" due to the fizzing and taste of Fentora...Fentora therapy was discontinued the next day with the event resolved. The consumer mentioned that he had tried using Fentora under his tongue on an unknown date.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5610851-3 2/1/2008	Wrong route	chronic non-cancer pain			Sublingual	No adverse event reported	... The patient's medical history and concurrent conditions included: chronic pain, infection, motor vehicle accident in 1998, occasional alcohol use, and she was an occasional smoker. The patient's weight was 165 pounds. She had previously experienced drug hypersensitivity when taking avelox and celebrex. Other medical history included no reported drug abuse or illicit drug use. The patient was treated with fentanyl-TTS (reservoir patch) at a dose of 12.5 ug/hr initiated on an unspecified date in SEP-2007 to NOV-2007 for chronic pain... The patient began using fentanyl-TTS approximately 3 years ago, on an unknown date the patient used a hairdryer to warm the application site for better adhesion, she also used alcohol on the application site for better adhesion..Concomitant medications included methadone, fentrinol for pain, and fluoxetine hydrochloride. At the time of this report, on an unknown date the patient had stopped using a hair dryer and alcohol for better adhesion and she had recovered from itching and nausea on [redacted] ...
5483526-1 10/10/2007	Wrong route	chronic non-cancer pain	400 mcg Actiq to 200 mcg Fentora		Sublingual	No adverse effect reported	A consumer report received regarding a male who initiated Actiq (oral transmucosal fentanyl citrate), 400 mcg, and was switched to Fentora (fentanyl buccal tablet) therapy, 200 mcg for the treatment of severe, non-cancer pain and reported using Fentora sublingually. The patient reported concurrent use of another opioid but declined to provide any further details. Therefore, it is not known if the patient was opioid tolerant. No further information was provided

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5519637-1 11/15/2007	Wrong route	Guillain Barre Syndrome			Sublingual	No adverse effects	A consumer report received regarding a male who initiated Fentora (fentanyl buccal tablet) therapy, 600 mcg (dates and frequency unknown) for the treatment of Guillian Barre syndrome... Two Fentora tablets did not dissolve after 30 minutes so the patient swallowed the remainder. Though the patient did receive instructions for proper use and disposal of Fentora, the patient takes Fentora by sublingual route of administration but has not experienced any untoward effects
5573969-X 12/21/2007	Wrong Route	mandibular joint pain		800 mcg	Sublingual	Lack of effect	...A consumer report received regarding a female who initiated Fentora (fentanyl buccal tablet) therapy, 800 mcg (dates and frequency unknown) for the treatment of mandibular joint pain. Concomitant medication included Opana (oxymorphone), morphine sulfate, and Oxycontin (oxycodone). The patient has been taking Fentora sublingually as prescribed by her physician. The patient was aware that this was not the recommended route of administration, but due to her mouth pain it was the only way that she could use Fentora. The purpose of the call was to report that the tablets did not dissolve within the normal amount of time and subsequently experienced lack of effect. The patient stated that she had a very dry mouth associated with her condition and believed that it may be contributory to the dissolution problem.

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5599081-1 1/18/2007	Wrong route	Migraines and back pain		400 mcg up to 5 times daily	Sublingual	Tongue ulceration	A consumer report received regarding a 48-year-old female who switched from Actiq (oral transmucosal fentanyl citrate) to Fentora (fentanyl buccal tablet) therapy, 400 mcg up to five times daily in Feb-07, for the treatment of migraines and back pain. Concomitant opioid medication included Oxycontin (oxycodone), 120 mg three times daily since 1997. Shortly after initiating Fentora, the patient experienced multiple application site ulcerations of the gums despite rotation of the sites. The physician suggested then placing the tablet sublingually, and her tongue subsequently became ulcerated and was bleeding from the tip. According to the consumer the physician was uncertain if the ulcers were caused by Fentora but had subsequently discontinued therapy and the ulcers resolved. One month later, Fentora was restarted by at a dose of 600 mcg. The patient reported the dose was too strong as it made her feel "dopey and loopy". The dosage was then reduced to 200 mcg but she was achieving an adequate clinical effect. On [redacted] the dosage was increased back to 400 mcg and within two days the mouth ulcers recurred. The patient had not developed the ulcerations or experienced bleeding while on the 200 mcg or 600 mcg dosages...

Off Label Use							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5501092-9 10/29/2007	Wrong route	reflex sympathetic dystrophy			Oral	No adverse effects	...A consumer report received regarding an adult female who initiated Fentora (fentanyl buccal tablet) therapy, (dosage unknown) for the treatment of reflex sympathetic dystrophy pain. Concomitant opioid therapy included Oxycontin 80 mcg three times daily. The patient reported that she had accidentally swallowed Fentora instead of taking via the buccal route as instructed because she "forgot". The purpose of the call was to inquire how long before she could take another dose by the correct route of administration. The patient was not symptomatic

Breakthrough Cancer Pain							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5444056-6 8/31/2007	Improper Frequency			400 mcg, every 2 hours as needed up to 8 times daily		Constipation, difficulty urinating, inability to stay awake, inability to eat and drink	A consumer report received regarding a 64-year-old male who initiated Fentora (fentanyl buccal tablet) therapy, 400 mcg every two hours as needed up to eight times daily on [redacted], for the treatment of breakthrough cancer pain (sarcoma). Subsequently the patient experienced a lack of effect stating that the pain relief did not last long enough. The patient had a history of difficulty urinating since being on narcotics and the reporter believed that Fentora had contributed to the problem. On [redacted], the patient took two tablets of Fentora simultaneously along with four 50 mcg/hr fentanyl patches and experienced slurred speech and was unable to stay awake. The event lasted approximately two hours and the patient described it as feeling like just had an anesthetic. Fentora therapy continued with the event of difficulty urinating ongoing...Follow-up information received from the patient's wife indicated that he experienced side effects all the time" while taking Fentora. In addition to the previously reported events, the patient also experienced an inability to have a bowel movement, an inability to stay awake, and an inability to eat and drink. These symptoms limited the patient's limited use of Fentora to eight tablets daily. The patient was never able to achieve adequate pain control while taking Fentora until he underwent insertion of a neurostimulator implant on [redacted]. Fentora was discontinued on an unspecified date and the events subsequently resolved.

Breakthrough Cancer Pain							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5475744-3 10/1/2007	Improper Patient No around-the-clock opioid therapy					No adverse effects reported	A report received from a registered nurse of the New York State Department of health regarding an unidentified patient who was prescribed Fentora (fentanyl buccal tablet) for the treatment of breakthrough cancer pain. The physician prescribed Fentora 800 mcg and 600 mcg, 112 tablets every 15 days and OTFC (oral transmucosal fentanyl citrate) 1600 mcg, 120 lozenges every 15 days for the treatment of breakthrough cancer pain. The patient had the prescriptions refilled within 10 days instead of 15 days... It was noted that no other opioids were prescribed for the patient's pain management. The caller was concerned regarding the size and number of doses used during the 10-day period.
5247435-5 2/22/2007	mcg for mcg		Actiq 1600 mcg to Fentora 1600 mg	1600 mcg twice daily		Pharmacist detected error and new prescription was written and dispensed	...The patient had previously taken Actiq (oral transmucosal fentanyl citrate) 1600 mcg twice daily for the treatment of breakthrough cancer pain. The patient's pain management therapy was switched from Actiq to Fentora...The patient reported that his physician wrote a prescription for Fentora 1600 mcg twice daily; however, the pharmacist detected the error. A new prescription for Fentora was written and dispensed for 400 mcg twice daily.

Breakthrough Cancer Pain							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5328039-2 5/15/2007	Wrong Route				Sublingual	Unknown	A report received from a female consumer who was prescribed Fentora (fentanyl buccal tablet) for breakthrough cancer pain on [redacted] The labeling instructions on the prescription stated the "place one tablet under the tongue four times per day." It was not known if the physician prescribed the route of administration or if the instructions were erroneously placed on the label at the pharmacy. However, the patient ended the call prior to obtaining physician and pharmacy information and therefore, further follow-up is not reasonably possible to obtain.

Unspecified Indication							
ISR # FDA Receipt Date	Type	Indication	Incorrect conversion from Actiq	Dose and Frequency	Route	Outcome	Narrative
5429154-5 8/28/2007	Improper frequency	Inappropriate dose (every 30 minutes)		400 mcg, every 30 minutes		Pharmacist intercepted error, new prescription written	...The patient had previously taken Actiq (oral transmucosal fentanyl citrate) 800 mcg for an unspecified indication. The patient's therapy was switched from Actiq to Fentora in approximately Mar-07. On [redacted], the pharmacist reported that the patient came into the pharmacy to fill her prescription for Fentora 400 mcg every 30 minutes...The pharmacist thought that the script had been written in error and planned on contacting the physician to correct it...after talking with the physician, the final prescription was for Fentora 400 mcg twice daily, may repeat once 30 minutes after starting the medication.
5328040-9 5/15/2007	Improper Frequency			800 mcg, three to six times daily		ER visit due to intentional overdose	...A report received from a physician, via a sales representative, regarding a 34-year-old female who initiated Fentora (fentanyl buccal tablet) therapy 800 mcg three to six times daily, on an unknown date, for an unspecified indication. On [redacted] the patient overdosed by taking 1/3 of a box of 800 mcg Fentora (approximately 10 tablets or 8000mcg) all at once. She subsequently passed out and was taken to the Emergency Room (ER). The patient recovered and is currently seeking treatment for abuse. Subsequent to this event, the prescribing physician discharged her from his care.
5326498-2 5/10/2007	Wrong Route				Not specified	No clinical effects expected	A report received via active surveillance of the American Association of Poison Control Centers database, NCSBeta (case #1) regarding a 69-yeard-old male who received Fentora (fentanyl buccal tablet), 100 mcg, via an incorrect dosing route on [redacted] The event was judged as a nontoxic exposure with no clinical effects expected. Additional information has been requested.

5326497-0 5/11/2007	Wrong Route				Not specified	No adverse events	A report received via active surveillance of the American Association of Poison Control Centers database, NCSBeta (case #2), regarding a female in her 60's, who received Fentora (fentanyl buccal tablet), 100 mcg, via an incorrect dosing route ion [redacted]. The error did not result in any symptoms. nformation has been requested.

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/s/

Mary Dempsey
4/8/2008 01:53:36 PM
DRUG SAFETY OFFICE REVIEWER

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4/8/2008 01:56:23 PM
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REVIEW
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Review: NDA 21-947/S005 Fentora (fentanyl buccal tablet, FBT), Supplemental New Drug Application (sNDA)

Indication: Management of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying persistent pain

Company: Cephalon, Inc

Submission: NDA 22-224 is located in the EDR. The submission includes a section titled 'Abuse Liability Assessment' (found under Module 5.3.5.4)

This review provides recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) regarding the abuse and diversion potential of Fentora.

Summary:

Cephalon, Inc. has filed this 505(b)(2) supplemental New Drug Application (sNDA 2 1-947) in support of registration of Fentora (fentanyl buccal tablet, FBT) C-II for the treatment of break-through-pain (BTP) in opioid tolerant non-cancer patients with chronic pain. Fentora is one of the most potent and rapidly absorbed μ opioid agonists currently approved for use in an unsupervised patient setting.

Background:

Fentora was initially approved on September 25, 2006, for the treatment of breakthrough pain in opioid tolerant patients with cancer with a proposed Risk Minimization Action Plan (RiskMAP) to minimize three identified risks: 1) use of the product by non-tolerant individuals; 2) misuse, abuse and diversion; and 3) unintended exposure.

sNDA 21-947 proposes five tablet strengths (100, 200, 400, 600 and 800 μg) for buccal mucosal administration and all are indicated for the management of breakthrough pain in patients with noncancer pain who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

Fentanyl is estimated to be one hundred times as potent as morphine as an analgesic (Gutstein and Akil in Goodman & Gilman, 11th Ed., 2006). Fentanyl is controlled in Schedule II of the Controlled Substances Act (CSA) as are similar opiates approved for medical use, including hydromorphone, morphine, and oxycodone. Schedule II drugs have the highest potential of abuse and pose a high risk to the public health (21 U.S.C. 812)

Review:

The Controlled Substance Staff (CSS) in CDER has expressed concern about the safety risks for addiction, abuse and diversion, as evidenced by data acquired during clinical development of FBT, and has asked the sponsor for additional information by which to evaluate these risks. This CSS review is preliminary, as assessment of data and other information submitted by the sponsor under NDA 21-947 is ongoing. This review is limited to issues concerning the potential abuse and diversion of FBT; as the general review of safety for an expanded indication in the proposed patient population is covered by DAARP.

Information included in this review includes general summary data provided by the sponsor, quarterly safety reports and the report submitted with the expanded indication entitled "Review and Assessment of Risks for Abuse and Diversion"(Report Approval Date: 2 November 2007).

FBT Phase 3 studies

Table 1 summarizes the Phase 3 studies for the new supplemental indication. Only two of the studies were conducted for periods consistent with long term administration in chronic noncancer pain: 3052, a 12 week double-blind, placebo-controlled study and the open label, uncontrolled study 3040. The sponsor uses the total number of patients evaluable for safety (i.e., 941) as the denominator in its report on review and assessment of risks of abuse and diversion.

Table 1: FBT Phase 3 Studies in Opioid-Tolerant Patients with Chronic Noncancer Pain and Breakthrough Pain

Study type & number	Population	Study duration	Number of patients
Double-blind, placebo-controlled studies:			
Study 3052	chronic noncancer pain	12 week	104
Study 3041	chronic neuropathic pain	< 4 weeks	79
Study 3042	chronic low back pain	< 4 weeks	77
Open-label, uncontrolled study:			
Study 3040	chronic noncancer pain	Up to 18 months	727
Total number of patients evaluable for safety			**941**

All patients entered the FBT studies while taking an around-the-clock (ATC) opioid and were managing BTP using an opioid. All patients were screened and required to meet protocol-specified entry criteria. In an attempt to screen out patients who might be at higher risk of abuse or addiction, those with a recent history (within 5 years) or current evidence of alcohol or substance abuse were excluded. In addition, all patients underwent a urine drug screen (UDS) and were excluded if there was evidence of an illicit substance or a medication for which there was no legitimate medical explanation. Patients could be excluded if in the opinion of the investigator, the patient had a psychiatric condition that would compromise their safety if they participated in the study. While there were no scheduled UDS during the study after the screening visit, investigators were permitted to conduct a UDS at anytime at their discretion.

Abuse Potential

The sponsor's report entitled "Review and Assessment of Risks for Abuse and Diversion" (Report Approval Date: 2 November 2007) reviews the events of abuse, addiction, and overdose that have been reported in FBT clinical studies of opioid-tolerant patients with chronic noncancer pain and BTP. A number of publications in the literature have identified aberrant drug-use

behaviors within patients with noncancer-related pain who were taking opioids (Table 2 lists these behaviors, as identified in the sponsor's review of the literature). The sponsor reviewed their clinical database retrospectively for evidence of these behaviors that may be precursors or signs for abuse. They considered the following behaviors as 'high risk': abuse/dependence, overdose and urine drug screen (UDS) that was positive for an illicit substance or a medication for which there was no legitimate medical explanation. The results of this evaluation are summarized in Table 3.

Table 2: Types of Aberrant Drug-use Behaviors (as identified by the sponsor)

Abuse/Dependence	Study drug theft
Overdose	Lost to follow-up
Motor vehicle accident	Seeking prescriptions from other sources
Fear of addiction	Lost study drug
Discharged from practice	Overuse of study drug
Positive UDS	Unapproved use of a medication used for another symptom
Unreliability	Acquiring opioids from other medical sources
Using nonprescribed medication	

Table 3: Summary of Patients by Risk Category

Risk Category	Number of Patients[¥]	Percent
High risk behaviors*	30	3%
Abuse/dependence	8	<1%
Overdose	9[#]	1%
Positive UDS	13	1%
Other Aberrant behaviors	126	13%
None	785	83%

[¥] Patients could have more than one aberrant behavior reported
*3 patients also had non-high risk aberrant behaviors
[#] includes one patient with 2 episodes of overdose

Overall, of the 941 patients in the safety analysis set, the sponsor reported that 3% of the FBT Phase 3 population exhibited 'high risk' behavior, and 17% (n=156) had at least one aberrant drug-use behavior. The majority of patients (132/156 or 85%) of these patients had only 1 behavior identified. The aberrant behaviors identified in more than 1% of patients in the safety analysis set were overuse of study drug (44 patients, 5%), study drug theft (35 patients, 4%), and lost to follow-up (33 patients, 4%) (Table 4).

Table 4: Aberrant Behaviors Identified in > 1% of Patients

Behavior	Number of Patients	Percent
Overuse of study drug	44	5%
Study Drug thefts	35	4%
Lost to follow-up	33	4%

In their conclusions, the sponsor indicated that the 17% incidence of adverse drug-use behaviors is lower than that reported in the observational studies in this population (Webster and Webster 2005; Chabal et al. 1997). They postulated that the difference was likely due to the differences between clinical studies and clinical practice. The sponsor's evaluation of possible baseline predictors of these behaviors revealed that younger patients and patients with a history of mania or psychosis were at higher risk of displaying one or more of the identified aberrant behaviors. Patients with a history of anxiety or mood disorders (prevalent conditions in this chronic pain population) did not appear to be at higher risk of having aberrant behaviors. Finally, the sponsor stated that the risk of developing an aberrant behavior was not affected by duration of treatment in the study.

Drug Diversion

During these clinical studies, thefts of drug from both individual patients and from the study centers were reported by the sponsor (Table 5). The sponsor noted thefts of study drug from 35 patients in studies 3040 and 3052, with no drug thefts occurring in the shorter duration studies (3041 and 3042). Police reports were made for 22 of the occurrences.

Table 5: Study drug thefts during the Phase 3 clinical trials

Study drug theft	Number of cases	Percent	Amount of drug stolen
From patient	35	4.2%*	----
From study center	5	---[+]	4,290,600µg[¥]

*Number of cases (5) divided by the total 831 patients (831) in studies 3040 and 3052.
[+]There were 69 study centers in study 3040
[¥]Calculated from additional information provided by the sponsor on 03/21/08, expressed in total µg - see below

Study site	Number of tablets	Strength µg/tablet	Total Amount of Drug (µg)
011	24	600	14400*
031	306	800	244800
036	1038	100	103800
	834	200	166800
	1038	400	415200
	1038	600	622800
	834	800	667200
031	24	100	2400
	24	200	4800
	432	400	172800
	942	600	565200
	1350	800	1080000
018	88	400	35200
	124	600	74400
	151	800	120800

*This study site also reported that '4 x 6' was stolen in addition to the 24 x 600µg tablets, but did not provide further information (.e.g., whether these are individual tablets or packs of tablets). Thus, the provided calculation might represent an underestimation of the amount of drug stolen.

The sponsor indicated that patients were withdrawn when the risk of diversion or repeat theft was thought to be high, although the criteria for high risk were not provided. Five patients were withdrawn from the study, four from study 3040, and one from study 3052. Most of the thefts (30 of 35) were reported to have been perpetrated by people who did not have regular access to study drug, and 20 of the thefts were reported to have occurred outside the patient's home. The husband of one patient, who reportedly took the patient's study drug, was found dead of a possible FBT overdose.

Despite significant protocol precautions designed to ensure the safe delivery, handling and storage of study drug in accordance with local and federal regulations, 5 study centers participating in study 3040 reported thefts of study drug, which were reported to local authorities and to the DEA. Study drug was taken from locked cabinets in 3 of the thefts, including one where there were signs of forced entry. The study drug was lost in transit from the health facility distribution center to the pharmacy in one theft, and in the remaining case, unused study drug returned by a patient was subsequently missing during a drug accountability/return review.

Comments on the Sponsor's Analysis of Abuse and Diversion Potential Data

Our preliminary review of the sponsor's data indicated additional cases of potential abuse than the 30 identified as "high risk" by the sponsor in their report "Review and Assessment of Risks for Abuse and Diversion". Thus, the sponsor's interpretation and conclusions concerning potential health risks of fentanyl buccal tablet when used in non-cancer break-through-pain (BTP) are not consistent with the CSS assessment and underestimate this risk. As such, on March 12, 2008, we requested that the sponsor provide the following:

- Complete information as to how data associated with "aberrant drug behavior" were gathered and evaluated, including the specific categories assigned to particular subjects in the data set.
- Criteria for determining a 'high risk' behavior
- Confirmation of the denominator data (number of noncancer patients exposed to Fentora in trials).
- Specific details on the instances of study drug stolen from the 5 participating study centers in study 3040, including reports filed with DEA.
- Case report forms and all available information on the cases listed in the attached Table.

On March 21, 2008, we received the sponsor's electronic response to this request. We note that our evaluations of this recent information are still ongoing, but we have the following comments.

In our most recent request to the sponsor, we asked for additional information, including information on specific cases that we had found among those coded as noncompliance or protocol violations. These cases were not part of those evaluated in the aberrant drug-use behavior report, and included those categorized as overuse of study medication and did not return study medication and/or packaging.

The sponsor responded that they limited their aberrant behaviors to those identified in clinical practice, as they found no information specific to the clinical trial setting. Accordingly, they did not consider protocol requirements to return unused study medication or packaging as indicative

of an aberrant behavior. Likewise, there were other protocol specific instructions of which noncompliance was not considered indicative of abuse or addiction. Consequently "reports of noncompliance were not automatically considered aberrant drug behaviors unless there was sufficient information to indicate an aberrant behavior that would be observed in a clinical practice setting." In addition, the sponsor provided new information on several other cases of aberrant behavior, not included in their original report.

CSS has contacted the DEA to confirm information on the thefts from the study sites reported by the sponsor. DEA had information regarding these cases, and provided information on other thefts of Fentora that have occurred from pharmacies, including an armed robbery. CSS is awaiting detailed information and confirmation of these additional cases.

Conclusions:

While we agree that most instances of noncompliance do not automatically indicate aberrant drug-use behavior or substance abuse, instances where a study drug is not returned as required does indicate a problem with drug accountability, which could potentially signify abuse or diversion. This is especially important for a Schedule II drug wherein accountability is a requirement of DEA registrants. Although we requested additional information on how the data was gathered, this information has not yet been provided.

We are particularly concerned about the training provided to the clinicians running these trials as to their recognition of behavior deemed "aberrant" and the policies and procedures for capturing and coding such behavior, including the definitions of addiction, abuse, and diversion employed in these studies. These types of information are essential to providing accurate information for assessing potential abuse and addiction occurring in these trials. Because this information is not available or perhaps was not gathered, the rates of abuse, diversion, and aberrant behaviors, in general, are likely underreported for these clinical trials. Furthermore, because most individuals who would be at high risk for substance abuse were excluded from participation in the Phase 3 clinical trials, the rates of these behaviors are not representative of what could occur if FBT were approved for expanded use in the general population with chronic pain.

Based on the information available to date, CSS finds that:

- The risks of unintentional potentially fatal overdose, as well as of misuse or abuse of fentanyl, and of FBT in particular, are extremely high, even when compared to risks posed by other transmucosal fentanyl products.
- Events observed in clinical trials illustrate the significant risks of overdose, misuse, abuse, and diversion from FBT. Detection of aberrant drug use behavior in the controlled setting of a clinical trial is very unusual and raises concern for the safe use of this drug in the general outpatient setting. It is particularly noteworthy in that "high risk patients" - those with a prior history of drug or alcohol abuse or those with a positive drug test - were excluded from participation in the clinical trials.
- It is of particular concern that aberrant drug use behavior in the sponsor's clinical trials appears to be much more frequent in the noncancer population who used Fentora long term.

- Finally, the signals obtained in postmarketing surveillance where the off label uses differed from the currently approved Fentora indication (treatment of breakthrough pain in opioid tolerant patients with cancer) resulted in serious adverse events, including deaths.

Taken together, these findings suggest that expanded use of this product will raise serious safety concerns, and additionally result in significant abuse and diversion that further impacts the public health and safety.

Abbreviations and Acronyms:

around-the-clock	ATC
break-through-pain	BTP
Controlled Substance Staff	CSS
Controlled Substances Act	CSA
Division of Anesthesia, Analgesia and Rheumatology Products	DAARP
fentanyl buccal tablet	FBT
Supplemental New Drug Application	sNDA

Date: April 1, 2008

Primary Reviewer: Lori Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff (HFD-009)

Secondary Reviewer: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Concurrence by: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

Summary of National Survey on Drug Use and Health (NSDUH)

NSDUH is the primary source of statistical information on the use of illegal drugs by the U.S. population. Conducted by the Federal Government since 1971, the survey collects data by administering questionnaires to a representative sample of the population through face-to-face interviews at the respondent's place of residence. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services, and is planned and managed by SAMHSA's Office of Applied Studies (OAS). Data collection is conducted under contract with RTI International, Research Triangle Park, North Carolina.[1]

NSDUH collects information from residents of households and noninstitutional group quarters (e.g., shelters, rooming houses, dormitories) and from civilians living on military bases. The survey excludes homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails and hospitals.

Since 1999, the NSDUH interview has been carried out using computer-assisted interviewing (CAI). Most of the questions are administered with audio computer-assisted self-interviewing (ACASI). ACASI is designed to provide the respondent with a highly private and confidential means of responding to questions to increase the level of honest reporting of illicit drug use and other sensitive behaviors and problems. Less sensitive items are administered by interviewers using computer-assisted personal interviewing (CAPI).

In addition to questions about the use of tobacco and alcohol, the survey obtains information on nine different categories of illicit drug use: use of marijuana, cocaine, heroin, hallucinogens, and inhalants; and the nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives. In these categories, hashish is included with marijuana, and crack is considered a form of cocaine. Several drugs are grouped under the hallucinogens category, including LSD, PCP, peyote, mescaline, mushrooms, and "Ecstasy" (MDMA). Inhalants include a variety of substances, such as nitrous oxide, amyl nitrite, cleaning fluids, gasoline, spray paint, other aerosol sprays, and glue. The four categories of prescription-type drugs (pain relievers, tranquilizers, stimulants, and sedatives) cover numerous pharmaceutical drugs available by prescription and drugs within these groupings that may be manufactured illegally, such as methamphetamine, which is included under stimulants. Respondents are asked to report only "nonmedical" use of these drugs, defined as use without a prescription of the individual's own or simply for the experience or feeling the drugs caused. Within the pain reliever category, specific questions about nonmedical use of Oxycontin are asked. Use of over-the-counter drugs and legitimate use of prescription drugs are not included.

Questions assessing substance use disorders, based on DSM-IV criteria, are included, as well as items on treatment for substance use problems. Mental health status and treatment are also covered in NSDUH.

The 2006 NSDUH employed a State-based design with an independent, multistage area probability sample within each State and the District of Columbia. The eight States with the

[1] RTI International is a trade name of Research Triangle Institute.

largest population (which together account for 48 percent of the total U.S. population aged 12 or older) were designated as large sample States (California, Florida, Illinois, Michigan, New York, Ohio, Pennsylvania, and Texas). For these States, the design provided a sample sufficient to support direct State estimates. For the remaining 42 States and the District of Columbia, smaller, but adequate, samples support State estimates using small area estimation (SAE) techniques. The design oversampled youths and young adults, so that each State's sample was approximately equally distributed among three age groups: 12 to 17 years, 18 to 25 years, and 26 years or older.

Nationally, 137,057 addresses were screened for the 2006 survey, and 67,802 completed interviews were obtained. The survey was conducted from January through December 2006. Weighted response rates for household screening and for interviewing were 90.6 and 74.2 percent, respectively.

Although the design of the 2002 through 2006 NSDUHs is similar to the design of the 1999 through 2001 surveys, there are important methodological differences that affect the comparability of the 2002-2006 estimates with estimates from prior surveys. In addition to the name change, each NSDUH respondent completing the interview is now given an incentive payment of $30. These changes, implemented in 2002 and continued subsequently, resulted in an improvement in the response rate, but also affected respondents' reporting of items that are the basis of prevalence measures produced each year. Comparability also may be affected by improved data collection quality control procedures that were introduced beginning in 2001 and by the incorporation of new population data from the 2000 decennial census into NSDUH sample weighting procedures. Analyses of the effects of these factors on NSDUH estimates have shown that 2002 and later data should not be compared with 2001 and earlier data from the survey series to assess changes over time.

A comprehensive set of tables, referred to as "detailed tables," is available through the Internet at http://www.oas.samhsa.gov. The tables are organized into sections based primarily on the topic, and most tables are provided in several parts, showing population estimates (e.g., numbers of drug users), rates (e.g., percentages of population using drugs), and standard errors of all nonsuppressed estimates. Additional methodological information on NSDUH, including the questionnaire, is available electronically at the same Web address.

Annual summary reports, brief descriptive reports and in-depth analytic reports focusing on specific issues or population groups are produced by OAS. A complete listing of published reports from NSDUH and other data sources is available from OAS. Most of these reports also are available through the Internet (http://www.oas.samhsa.gov). In addition, OAS makes public use data files available to researchers through the Substance Abuse and Mental Health Data Archive (SAMHDA, 2007) at http://www.icpsr.umich.edu/SAMHDA/index.html. Currently, files are available from the 1979 to 2006 surveys. The 2007 NSDUH public use file will be available by the end of 2008.

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Drug Abuse Warning Network

The Drug Abuse Warning Network (DAWN) provides information on some of the medical consequences of substance use, misuse, and abuse that manifest in visits to hospital emergency departments. DAWN records substances associated with drug-related emergency department visits; provides a means for monitoring drug misuse and abuse patterns, trends, and the emergence of new substances; assesses some of the morbidity associated with drug misuse and abuse; and generates information for national, State, and local drug policy and program planning. DAWN is also a tool that is increasingly being utilized for postmarketing surveillance and risk management for the pharmaceuticals regulated by the Food and Drug Administration (FDA). DAWN is the responsibility of the Office of Applied Studies, a Federal statistical unit within the Substance Abuse and Mental Health Services Administration (SAMHSA).

A new data collection protocol was introduced for DAWN in 2003. The new design addressed many longstanding limitations associated with DAWN data. Because virtually every feature of DAWN changed with the redesign, data from 2004[1] and beyond are not comparable to data from 2002 and prior years.

DAWN relies on a national probability sample of non-Federal, short-stay, general hospitals that operate 24-hour emergency departments. Hospitals are oversampled in selected metropolitan areas and divisions, and a remainder sample covers hospitals in the remainder of the U.S. Based on data from sampled units, national estimates of drug-related emergency department visits for the U.S. are produced annually.

DAWN estimates for 2006 are based on a sample of 544 eligible hospitals, with 160 (28% to 70%) responding in oversample areas and 45 (23%) responding in the remainder area. Estimates reflect adjustments for the stratified sample design, unit nonresponse, and nonresponse within a facility. Whether an oversample area stands alone in the national estimate depends on its response rate and the potential for nonresponse bias. At this time, comparisons over time are available only for 2004, 2005, and 2006.

In addition, authorized users in DAWN member hospitals; Federal, State, and local public health agencies, including SAMHSA and FDA; and pharmaceutical firms receive access to the raw DAWN case data, in de-identified form, as the DAWN cases are submitted. This surveillance of sentinel events is possible through a secure, Internet-based query system called DAWN *Live!*

To collect the data, each hospital emergency department that participates in DAWN has one or more reporters who review emergency department medical records retrospectively to find DAWN cases. Cases reported to DAWN include emergency department visits caused by or related to drug use for patients of any age. The drug use must be recent; chronic effects and history of drug abuse are not reportable. Visits related to drugs used for therapeutic purposes, as well as drug misuse and abuse, are all included.

[1] Data from 2003 represent a transition year that is not comparable to prior or subsequent years.

For each reportable visit, demographic, visit, and drug characteristics are abstracted from the medical record. Each DAWN visit is classified into one of eight case types: drug-related suicide attempt, those seeking detoxification or substance abuse treatment services, underage alcohol use (with no other drug involved), adverse reactions to pharmaceuticals taken as prescribed, overmedication when the dose of a prescription or over-the-counter medication or dietary supplement was exceeded, malicious poisonings, accidental ingestions when a drug was used accidentally or unknowingly, and all others, including explicit drug abuse. This classification and the drugs reported to DAWN are used to derive analytic subgroups (e.g., for visits involving illicit drug use, alcohol use, or nonmedical use of pharmaceuticals) for a variety of purposes and audiences. Other data items characterize drug-related visits in terms of diagnoses or disposition.

DAWN captures very detailed drug information. As many as 16 drugs plus alcohol are reported for each DAWN case. Drug-related emergency department visits often include multiple drugs, on average, 1.6 drugs per visit. For adults, alcohol is reportable only when present with another reportable drug; for minors, alcohol is always reportable. Drug information is captured at the level of detail present in the medical record. The same drug may be reported to DAWN by brand, generic, chemical, street, or nonspecific name, depending on the completeness and specificity of information in the medical record. Training and automated rules prompt DAWN reporters to use all available documentation in the medical chart to record drugs by their most specific names (e.g., OxyContin, when documented as such, instead of oxycodone), not to record the same drug by different names (e.g., heroin and opiates), and to exclude current medications unrelated to the visit. Estimates are published at the generic level (e.g., acetaminophen-hydrocodone), for specific ingredients (e.g., dextromethorphan), or by drug category (e.g., opiates/opioids, benzodiazepines). Estimates attributed to particular brand or trade names (e.g., Concerta®) are generally not published.

Since data for DAWN are extracted from a retrospective review of medical records, no patients or health care providers are interviewed. Health care settings within the hospital but outside of the emergency department, or emergency facilities outside of hospitals, are not covered. Laboratory findings to detect the presence of a drug are not recorded for DAWN cases, although each drug report has an associated indicator for whether the drug was confirmed by toxicology testing. Only the patient's own drug use is considered, a patient's intent to misuse or abuse a drug is not a factor in the DAWN case determination, and source of the drug is not captured because it is so rarely available in medical records. Repeat visits by the same individual cannot be linked together. Visits due to chronic conditions associated with a history of drug abuse are explicitly excluded. While DAWN does not collect direct identifiers, such as patient name, the content of the case data does render the data individually identifiable, and individually identifiable data are protected by Federal law from disclosure without consent.

DAWN does not measure the prevalence of drug abuse in the population, and external factors unrelated to the level of drug abuse in the population may contribute to the likelihood that a person presents to a hospital emergency department for a drug-related problem. For example, the availability of health insurance and/or other sources of care may influence whether an individual seeks care in an emergency department. Purity, experience, or other factors related to the physiological effects of drugs may affect whether a condition occurs to give rise to an emergency department visit.

DAWN also collects data on drug-related deaths reviewed by medical examiners and coroners (ME/Cs) in selected metropolitan areas and selected States. The death investigation jurisdictions that participate in DAWN do not constitute a statistical sample nor is every jurisdiction within a metropolitan area necessarily a participant. As a result, extrapolation of drug-related deaths to the Nation as a whole is not possible, and metropolitan area totals are only possible if all jurisdictions within the area participate. The number of jurisdictions that participate in DAWN varies from year to year. In 2003, the last year for which mortality data have been published, 122 jurisdictions in 35 metropolitan areas and 126 jurisdictions constituting six States participated in DAWN. The case criteria and data collection procedures for drug-related deaths mirror those used in emergency departments. Causes and manner of death are captured, in lieu of case type and diagnoses.

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Treatment Episode Data Set

The Treatment Episode Data Set (TEDS) provides information on the demographic characteristics and substance abuse problems of clients admitted to treatment for abuse of alcohol and drugs in the United States. The information in TEDS is compiled from State administrative systems and is collected by the States from those treatment facilities that they monitor or fund. TEDS records represent admissions rather than individuals, as a person may be admitted to treatment more than once. Approximately 1.8 million admissions records are submitted to TEDS each year. TEDS is maintained by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA).

While TEDS does not represent the total national demand for substance abuse treatment, it does comprise a significant proportion (an estimated 80 percent) of all admissions to substance abuse treatment, and largely includes those admissions that are subsidized by public funds. Differences in State systems of licensure, certification, accreditation, and disbursement of public funds affect the scope of facilities included in TEDS. Treatment facilities that are operated by private for-profit agencies, hospitals, and State correctional systems, if not licensed through the State substance abuse agency, may be excluded from TEDS. TEDS does not include data on facilities operated by Federal agencies (the Bureau of Prisons, the Department of Defense, and the Veterans Administration).

TEDS data on treatment admissions include:

- demographic information
- primary secondary and tertiary substances of abuse, their route of administration, frequency of use, and age at first use
- source of referral to treatment
- number of prior treatment episodes
- service type, including planned use of methadone.

Among the substances of abuse collected in TEDS are opiates. This category is further broken down into three subcategories: heroin, non-prescription methadone, and other opiates/synthetics. "Other opiates" is comprised almost entirely of opioid analgesics. While admissions involving use of "other opiates" represent a very small proportion of total TEDS admissions (4.2% in 2006), in the past decade, there has been a dramatic increase in the admissions for drugs in this category. Most of this growth has occurred since 1997. From 1997-2006, total admissions increased 12%, admissions in which heroin was the primary substance of abuse increased 4% and admissions in which "other opiates" were the primary substance increased 367%.

	1997		2006	

	N	%	N	%
Total admissions	1,607,957	100.0	1,800,717	100.0
Heroin admissions	235,143	14.6	245,984	13.7
Other opiates	16,274	0.1	74,750	4.2

Admissions for "other opiates" are primarily white and somewhat more likely to be male than female (57% versus 43%). The increase in admissions for "other opiates" between 1997 and 2006 were greatest among the youngest age groups, especially 15-19 years and 20-24 years.

TEDS is an exceptionally large and powerful data set. Like all data sets, however, care must be taken that interpretation does not extend beyond the limitations of the data. Limitations fall into two broad categories: those related to the scope of the data collection system, and those related to the difficulties of aggregating data from the highly diverse State data collection systems. Limitations to be kept in mind while analyzing TEDS data include:

- TEDS is an admission-based system and TEDS admissions do not represent individuals. An individual admitted to treatment twice within a calendar year would be counted as two admissions. Many States cannot, for reasons of confidentiality, identify clients with a unique ID assigned at the State level. Consequently TEDS is unable to follow individual clients through a sequence of treatment episodes.
- TEDS attempts to enumerate treatment episodes by distinguishing the initial admission of a client from his/her subsequent transfer to a different service type (for example, from residential treatment to outpatient) within a single continuous treatment episode. However, States differ greatly in their ability to identify transfers; some can distinguish transfers within providers but not across providers. Some admission records may in fact represent transfers, and therefore the number of admissions reported probably overestimates the number of treatment episodes.
- The number and client mix of TEDS admissions does not represent the total national demand for substance abuse treatment, nor the prevalence of substance abuse in the general population.
- The primary, secondary, and tertiary substances of abuse reported to TEDS are those substances which led to the treatment episode, and not necessarily a complete enumeration of all drugs used at the time of admission.

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Briefing Document for the Anesthesia and Life Support Drug Advisory Committee Meeting

May 6, 2008

Fentora®
NDA 21-947
Supplement 005

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products

Silver Spring, MD 20993

Executive Summary

The purpose of this Advisory Committee meeting is to discuss the supplemental new drug application for Fentora® [fentanyl buccal tablet], proposed for the indication of "management of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying persistent pain." Fentora® was approved on 25 September 2006 with an indication of "the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain." The first product approved with this indication was Actiq, which now has generic versions. Actiq, formulated as a lozenge on a stick, was approved under Subpart H, to reflect the particular hazards of the product to household contacts, particularly children.

The applicant also proposes modifying the labeling that describes opioid-tolerance from what is currently in the package insert from:

> "...patients who are **already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking around-the-clock opioid medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer"

to:

> "...patients who are regularly taking around-the-clock opioid medicine for their underlying persistent pain."

We ask the Committee to consider the open issues identified in the narrative below in its deliberations over the need for additional information about this product.

The clinical development program for this supplement was conducted in the United States and consists of data from four key studies. Study 3052 was intended to support a finding of efficacy for the new indication. This was a study of unconventional design in which opioid-tolerant patients without cancer received open-label Fentora for a total of 12-weeks. Patients were required to have from one to four episodes of breakthrough pain each day. Following Weeks 4, 8, and 12 of open-label therapy, there were blocks of randomized, placebo-controlled, dosing where the efficacy of the drug was studied. Studies 3041 and 3042 were short-term randomized, placebo-controlled, nine-period crossover studies in patients with BTP in the setting of neuropathic pain and chronic low back pain, respectively. Study 3040 was an open-label, long-term safety study, also in patients without cancer.

At the time of finalization of this Briefing Document, we have reviewed Study 3052, provided an estimate of the numbers of new patients eligible for Fentora® were it to be

approved and conducted a comparative safety analysis, using the available safety data from the studies that enrolled cancer patients.

At this point in our, the data appear to support a finding of efficacy for the new indication. However, we are concerned that the safety data show an excess of serious and non-serious adverse events attributable to the CNS effects, respiratory depression, and addiction potential of opioids in the non-cancer population as compared to the data from similarly designed studies with the cancer population. We request that the committee discuss the risks and benefits of an approval of the use of Fentora® in patients without cancer.

Summary of FDA Review of Clinical Efficacy & Safety

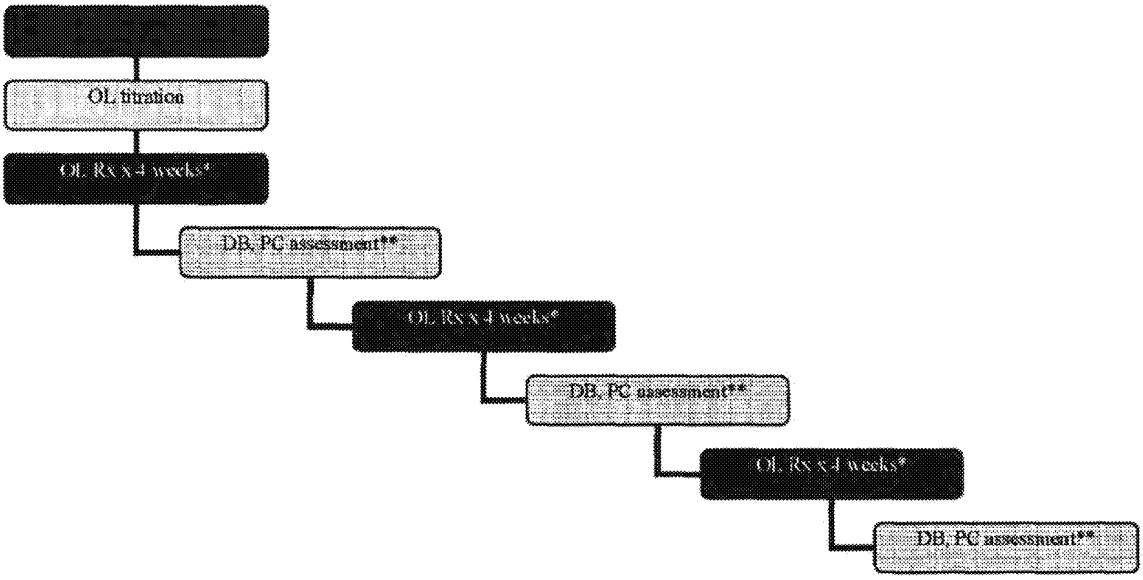
Efficacy

The applicant submitted three studies to support a finding of efficacy in patients with breakthrough pain who are on ATC opioids for their chronic pain. The primary study is Study 3052 since it assessed efficacy over 12-weeks, the duration usually required for a chronic indication. Studies 3041 and 3042 provide supportive data but were very short term studies.

Study 3052

This was a study in opioid-tolerant patients with a variety of non-cancer pain etiologies that had three placebo-controlled, double-blind, crossover assessment periods and three open-label periods spaced throughout the study. The study enrolled opioid-tolerant adults with chronic pain (of at least three months duration) who were experiencing 1-4 episodes of BTP/day. Patients with a history of substance abuse were to have been excluded.

The study was divided into eight blocks, shown schematically below.



Briefly, 199 patients were screened. One hundred and forty-eight patients entered an open-label dose finding period with the goal of a single tablet of Fentora providing analgesia such that a rescue dose was not required. A successful dose was achieved in 103 patients who entered the first 4-week open-label treatment block.

Patients were treated with the successful dose for four weeks. Following the first open-label treatment block, patients entered a 9-period, double-blinded, placebo-controlled assessment period. For the assessment period, patients were dispensed nine numbered doses to be self-administered in order. Each sequence consisted of 6 active and 3 placebo tablets. The placebo was distributed among the active doses with three possible sequences used. Immediately prior to dosing and for 120 minutes following each dose in the assessment period, patients were to record pain scores (intensity and relief).

The open-label treatment and double-blind assessment blocks were repeated twice more for a total study length of 12-weeks (excluding screening and the initial dose-finding blocks).

The primary efficacy endpoint was a comparison of the summed pain intensity difference over 60 minutes ($SPID_{60}$) for the active and placebo treatments, from the double-blind assessment period, following the third block of open-label therapy. There were multiple secondary endpoints, many of which were calculated from the raw pain intensity and pain relief scores but also included quality of life scales and patient and clinician global assessments.

The study met the objective, with a statistically significant difference in the $SPID_{60}$ at 12 weeks that favored Fentora ($p<0.0001$). The summary statistics are shown below.

Variable Statistic	OVF (N=79)	Placebo (N=79)
Mean SPID 60 minutes posttreatment per patient		
n	79	79
Mean	7.7	4.6
SD	6.15	4.73
SE of mean	0.69	0.53
Median	6.4	4.4
Min, max	–0.1, 28.7	–1.5, 24.1
Mean SPID 60 minutes posttreatment per episode		
n	453	226
LS mean	7.63	5.19
SE of LS mean	0.56	0.69
p-value	<0.0001	—
LS mean of (OVF–Placebo)	2.44	—
95% CI (OVF–Placebo)	1.3, 3.58	—

SOURCE: Summary 15.22; Listing 13, and Listing 14.
SPID=summed pain intensity differences; OVF=ORAVESCENT fentanyl; SD=standard deviation; SE=standard error; min=minimum; max=maximum, LS=least squares; CI=confidence interval.
NOTE: The LS mean, SE of LS mean, and p-value for the treatment comparison are from an analysis of variance (ANOVA) based on individual episodes with treatment as randomized, episode, sequence, and carryover as fixed factors, and patient as a random factor, using compound symmetry.

Source: Applicant's Clinical Study Report

The applicant conducted a permutation test to assess whether the non-random sequences used in the double-blind assessment blocks affected the result. The permutation test showed that there was no sequence effect.

With the exception of the "Work Productivity and Activity Impairment instrument" the secondary endpoints supported the primary although the applicant did not make any statistical adjustment for multiple comparisons and did not provide any data to support the significance of many of the questionnaires used.

At this point in our review, we are in substantial agreement with the applicant that Fentora was effective over 12 weeks of therapy.

Study 3041 and Study 3042

These two studies had an open-label titration period followed by one randomized, double-blind, placebo-controlled, nine-period crossover dosing period of the same design as the double-blind, placebo-controlled assessment periods noted above. The patient population for Study 3041 was opioid-tolerant adults with chronic neuropathic pain. The population for Study 3042 was opioid-tolerant adults with chronic low back pain. Upon a preliminary review, the results of these studies were consistent with Study 3052.

Safety

The safety review of the new Fentora data was still in progress at the time the briefing package was due. This summary represents the findings to date.

General comments about FDA's approach to safety for this application

The review of safety for this product is not straightforward because of the nature of the investigational product, level of detail of the adverse event reports, and the population studied. By definition, these patients are on around-the-clock opioids. The study drug is fentanyl, an opioid without pathognomonic adverse events via the transmucosal route. In the clinical development program, the applicant collected safety data appropriate for a Phase 3 study of a reformulated opioid (adverse events, vital signs, clinical laboratory tests, physical exam). The applicant included oral cavity exams and urine toxicology screens because of the nature of this product and patient population studied.

There are limitations to the safety data collected. The exact time of Fentora administration and exact time of adverse event onset was not documented. However, as patients were self-medicating at home over a 12-week period of time, for the vast majority of the safety data, that level of detail is difficult to collect reliably. As patients were on different background opioids, and were on different doses of background opioids, it can be difficult to determine whether common opioid adverse events were attibutable to study drug or background therapy.

Summary of available, pertinent data

To augment the relatively small numbers and treatment durations of Studies 3041, 3042, and 3052, the applicant conducted Study 3040, an 18-month, open-label safety study in opioid-tolerant, non-cancer patients with BTP. Study 3040 enrolled de novo patients (81%) and rolled over patients who completed Studies 3041 and 3042 (19%). The de novo patients underwent a dose-finding period prior to stable dosing. Study 3040 collected data on safety as well as quality-of-life questionnaires. A total of 730 patients participated in Study 3040. The mean duration of exposure was 292 days with a median of 301 days. Most patients (83%) titrated to a 600 or 800 mcg dose.

The applicant's approach to the evaluation of safety in this supplement was to collect, analyze, and tabulate safety data for the non-cancer population. The applicant found that the adverse event profile was typical for an opioid and acknowledged the mucosal irritation that is associated with Fentora. While the applicant concluded that the safety and tolerability profile was similar to the opioid-tolerant patients with cancer, this comparative analysis was not presented in the NDA.

The applicant had conducted, completed, and submitted data for three clinical studies in the cancer population, Studies 14 and 15 in support of the original application and Study 3039. Studies 14 and 3039 were short term studies, typically lasting less than two weeks in total duration. Study 15 was conceptually similar to Study 3040 in that it was an open-label safety study that enrolled both rollover patients from Studies 14 and 3039 (122 patients) and de novo patients (75). The mean duration of time-on-trial was 158 days

with a median of 99 days. Since data meeting the applicant's quality standards for FDA submission are available for the cancer and non-cancer populations, a comprehensive comparison of the safety profile of Fentora in both populations is an important analysis to understand the risk in the new population. The non-cancer data should be viewed in that context.

FDA Safety Review

FDA conducted its comparative review of the cancer and non-cancer safety data in two major parts.

1. Comparison of demographic information and concomitant medication use.
2. Comparison of the adverse events in both groups. AsFentora was added to a background of opioid therapy in these studies, findings from the basic safety assessments, vital signs, laboratory, physical exams, were difficult to determine if attributable to study drug or background opioids. Furthermore, during the short-duration, placebo-controlled portions of the studies, an active dose and a placebo dose may have been self-administered on the same day. Last, detailed accounting of the timing of Fentora administration and adverse event onset was not adequate to definitively establish causality of events.
3. In our comparative analysis, we also took into account the comorbidities associated with advanced malignancies and cancer therapy. Therefore, terms such as anemia, weight loss, infection, etc. were not compared. What were compared between the groups were events such as overdose, respiratory depression, syncope, addiction, coma, those due to psychotropic effects, medication errors, and abuse. In this context, we examined three sets of adverse event data: serious adverse events, non-serious events that were classified as moderate to severe in severity, and common adverse events

Demographic information and concomitant medications

Table 1 summarizes pertinent data for the two groups.

Table 1: Summary of demographic and concomitant medication data

Parameter		Non-Cancer** [n (%)]	Cancer* [n (%)]
N		941	484
Age (years)	Mean	48.7	55.9
	Std. Dev	9.86	12.2
	Range	20-77	24-95
Race	Caucasian	874 (93)	407 (84)
	African-American	47(5)	29 (6)
	Other	20(2)	48 (10)
Sex	Male	407 (43)	227 (47)
	Female	534 (57)	257 (53)
ATC Opioid dose†	Mean	239.7 mg	342.1 mg
	Std. Dev	219.4 mg	407.6 mg

	Range	20-2160 mg	24-4800
Proportion taking concomitant CNS depressant drugs‡	Benzodiazepine	43%	38%
	Non-benzodiazepine sleep aid	21%	16%
	Tricyclic antidepressant	14%	7%
	Muscle relaxant (cyclobenzaprine, carisoprodol, etc.)	46%	10%
	Barbiturates	<1%	<1%
	Gabapentin or pregabalin	24%	15%
	Other	31%	20%

*Source – Merged datasets from Studies 14, 15, and 3039
**Source – Summary of Clinical Safety, current submission
†in morphine equivalents
‡Taking drug for >50% of time-on-trial

The non-cancer patients were younger and on a lower total ATC opioid dose although the non-cancer patient was more likely to be on another CNS depressant.

As Table 1 shows, there was more than twice the number of non-cancer patients than cancer patients in the databases. For the large safety studies, the mean duration of treatment was also longer for the non-cancer patients. The risk of experiencing an adverse event resulting in discontinuation is related to the total time-on-trial. Therefore, to normalize for risk of experiencing an adverse event, the Division requested that the applicant calculate the total time-on-trial for both groups.

The applicant found that the non-cancer population had 673.6 patient-years (PYR) of time-on-trial versus 128.0 PYR for the cancer population.

Serious adverse events

The serious adverse events (SAE) database was assessed. For this analysis, verbatim terms such as overdose, respiratory failure, coma, unresponsive, cyanosis, drug dependence, etc. were selected. We found no case that met the regulatory definition of "serious" that appeared to be due to overdose, withdrawal, or misuse of the drug in the cancer database. For example, in the cancer database, there were several cases of respiratory failure. However, they all appeared related to the underlying disease (bilateral malignant pleural effusions or similar). There were multiple examples of accidental overdose or SAEs related to abuse of the drug in the non-cancer population as summarized in Table 2.

Table 2: Serious adverse events related to overdose, abuse, misuse

	Non-cancer Population	**Cancer Population**
Total N	941	484
Accidental overdose	8	0

SAE related to drug dependence/withdrawal/abuse	2	0
SAE possibly related to oversedation (MVA with severe CNS and orthopedic injury where patient was the driver)	1	0

Non-serious, moderate-to severe intensity events

The adverse events databases for the pooled cancer and non-cancer populations were searched. Events that were not serious, but were of moderate to severe intensity, and opioid-related or related to the psychotropic effects of opioids were selected by verbatim term. There were a number of verbatim terms that appeared to represent similar adverse events, for example, there were reoprts of sleepy, sleepiness, excessive sleepiness, feeling sleepy and somnolent. These were pooled under the group sedation along with other related terms in order to get a sense of the frequency of particular events. The pooling strategy shown in Table 3 was employed.

Table 3: Pooling Strategy

Pooled Term	Verbatim Terms Contained
Dizzy	Dizziness, dizzy, intermittent recurrent dizziness
Lightheaded	Lightheaded, lightheadedness, intermittent recurrent lightheadedness
Seizures	Seizures
Syncope	Syncope, loss of consciousness
Sedation	Excessive opiate-related sedation, excessive sedation, somnolent, sleepiness, drowsy, sleepy, drowsiness, somnolence, excessive daytime sleepiness, lethargic, sluggish, excessive sleepiness, over sedation, feeling sleepy
Confusion	Confusion, confused, disoriented, intermittent confusion, disorientation, mental status changes, cognitive disturbance, worsening mental status, delirium, feeling spacey, change in mentation, delusions, absent short term memory, intermittent confusion, increased confusion, medication intoxication, intoxicated feeling, forgetfulness, could not focus mentally, mentally unfocused, lack of mental alertness, lack of concentration
Likability of opioid	High feeling, euphoria, intoxicated feeling, feeling spacey, medication intoxication, slurred speech
Fall	Fall, patient fell down, patient fell, fall at home, fell, fell down stairs, multiple falls, accidental fall
Withdrawal	Drug withdrawal symptoms, withdrawal symptoms, opioid withdrawal symptoms,
Fracture	Fracture [of specific bone(s)]
Addictive behavior	No pooling done
Substance abuse	No pooling done
Personality change	No pooling done
Six cracked bottom front teeth	No pooling done
Paranoia	No pooling done
Acute depression	No pooling done
Car accident	No pooling done

Intermittent inability to focus eyes	No pooling done
Impaired balance	No pooling done
Coma	No pooling done
Inability to close bilateral eyes completely	No pooling done
Physical trauma	No pooling done

Table 4 is the pooled data analysis where duplicate events are deleted. That is, if a patient experienced dizziness on > 1 occasion, it is only counted once here. However, if a patient experienced different classes of adverse events, that is captured. For example, if Patient 101 experienced 3 episodes of "dizziness," 1 episode of "dizzy," 2 episodes of "confusion" and 1 episode of "disorientation," that is counted as 1 dizzy and 1 confusion. The heavy bar separates events where the rate is higher for the non-cancer patients (above the bar) versus where the rate is higher in the cancer patients.

Table 4: Non-serious adverse events, moderate or severe in severity, related to CNS depression, psychotropic effects, or respiratory depression, duplicates deleted

	Non-Cancer N=941		**Cancer N=484**	
Pooled Term	**n**	**%**	**n**	**%**
Syncope	4	0.4	1	0.2
Sedation	61	6.5	14	2.9
Likability of opioid	7	0.7	2	0.4
Fall	19	2.0	7	1.4
Withdrawal	12	1.3	1	0.2
Fracture	17	1.8	0	0
Addictive behavior	1	0.1	0	0
Substance abuse	1	0.1	0	0
Personality change	1	0.1	0	0
Six cracked bottom front teeth	1	0.1	0	0
Paranoia	1	0.1	0	0
Acute depression	1	0.1	0	0
Car accident	1	0.1	0	0
Intermittent inability to focus eyes	1	0.1	0	0
Impaired balance	1	0.1	0	0
Coma	1	0.1	0	0
Inability to close bilateral eyes completely	1	0.1	0	0
Physical trauma	1	0.1	0	0
Dizzy	22	2.3	32	6.6
Lightheaded	10	1.1	13	2.7
Seizures	0	0	1	0.2
Confusion	14	1.5	10	2.1

Table 4 shows that, corrected for duplicate events and numbers of patients in the groups:

- Cancer patients had a higher prevalence of dizziness, lightheadedness, seizure, and confusion.
- Non-cancer patients has higher rates of most of the other pooled classes including sedation, falls, drug withdrawal episodes, fractures, and accidents. While there was only one case of each, only the non-cancer population had adverse events such as addictive behavior, substance abuse, and unusual incidents such as broken teeth.
- It should be noted that, excepting "coma" and "inability to close bilateral eyes completely" which occurred in the same patient, each of the unpooled terms occurred in a discrete patient.

Table 5 is the identical analysis where duplicate events have not been deleted. The time-on-trial is used to normalize in this analysis. Again, the heavy bar separates events where the rate is higher for the non-cancer patients (above the bar) versus where the rate is higher in the cancer patients.

Table 5: Non-serious adverse events, moderate or severe in severity, related to CNS depression, psychotropic effects, or respiratory depression, duplicates not deleted, normalized for time-on-trial

	Non-Cancer N=941 PYR = 673.6		**Cancer N=484 PYR = 128.0**	
Pooled Term	**n**	**rate per 100 pt-yr**	**n**	**rate per 100 pt-yr**
Withdrawal	12	1.8	1	0.008
Fracture	23	3.4	0	0
Addictive behavior	1	0.15	0	0
Substance abuse	1	0.15	0	0
Personality change	1	0.15	0	0
Six cracked bottom front teeth	1	0.15	0	0
Paranoia	1	0.15	0	0
Acute depression	1	0.15	0	0
Car accident	1	0.15	0	0
Intermittent inability to focus eyes	1	0.15	0	0
Impaired balance	1	0.15	0	0
Coma	1	0.15	0	0
Inability to close bilateral eyes completely	1	0.15	0	0
Physical trauma	1	0.15	0	0
Sedation	78	11.6	15	11.7
Dizzy	27	4.0	42	32.8
Lightheaded	10	1.5	10	7.8
Fall	20	3.0	8	6.3
Seizures	0	0	1	0.8
Syncope	4	0.6	1	0.8
Confusion	16	2.4	12	9.4

Likeability of opioid	8	1.2	2	1.6

Table 5 shows that, compared to Table 4 (uncorrected for duplicate events), in the cancer population, the prevalence of sedation, fall, syncope, and opioid -likability exceeds that of the non-cancer population. In this second analysis, the higher incidence of certain events conceivably related to misuse and abuse of the drug remain higher in the non-cancer population.

Common adverse events

Table 6 shows the rates of the common opioid-related adverse events in both groups.

Table 6: Common adverse events

Adverse event	Cancer* [n (%)]			Non-Cancer** [n (%)]
Study	14	15	3039	3040, 3041, 3042, 3052
N	123	232	125	941
Nausea	27 (22)	86 (37)	16 (13)	222 (24)
Vomiting	13 (11)	52 (22)	8 (6)	113 (12)
Constipation	10 (8)	33 (14)	7 (6)	67 (7)
Pruritis		7 (3)		
Dizziness	27 (22)	46 (20)	14 (11)	107 (11)
Somnolence	12 (10)	30 (13)		95 (10)
Confusion		15 (6)		
Application site complaints		15 (6)	12 (10)	116 (12)

*Source – Tables from individual study reports

**Source – Summary of Clinical Safety, current submission

Safety summary

- The comparative analysis of safety in patients with and without cancer shows that there is an excess risk of events related to overdose, addiction, and CNS depression related to opioids in the non-cancer population.
- The non-cancer patients are more likely to be on additional CNS depressant agents.
- Despite higher average opioid requirements, cancer patients do not appear to suffer the rates of medication errors, substance abuse, overdose, etc.
- The rates of common, non-serious opioid-related adverse events appear comparable between the groups.

Summary of FDA Review of Other Pertinent Data

Estimate of additional use if this supplement were approved

The applicant proposes an expanded indication for Fentora which implies a larger prescriber and patient base and larger quantities of drug on the market. It is difficult to estimate how much more Fentora is likely to be manufactured, prescribed, used, and abused if this supplement were to be approved. In this application, the applicant did not

make an estimate of the increased quantities of Fentora implied by the expanded indication. We made an estimate of the potential increased use as explained below.

1. According to "Cancer Facts & Figures 2007," http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf there are 10.5 million Americans who have ever had cancer. In 2007, Marieke et al[12] published a study that examined the number of cancer patients with pain in the Netherlands. These researchers found that 351 of 1429 patients reported moderate to severe pain. On the basis of these sources, approximately 2,580,000 Americans have moderate to severe cancer pain. The references previously discussed found the percentage of cancer patients with breakthrough pain to be 51%, 63% and 89%. Therefore, a crude estimate of the number of cancer patients in the US with moderate to severe pain and BTP (therefore candidates for Fentora) is 10,500,000 x (351/1429) x 0.67 = 1,728,000.
2. According to the American Pain Society http://www.ampainsoc.org/links/roadblocks/conclude_road.htm approximately 9% of the US adult population experiences moderate to severe non-cancer chronic pain. The current US population is approximately 300,000,000. The previously described references estimated that 63% and 74% of non-cancer patients experience BTP. Therefore, a crude estimate of the number of non-cancer patients in the US with moderate to severe pain and BTP (therefore candidates for Fentora) is 300,000,000 x 0.09 x 0.68 = 18,360,000.
3. Therefore, based upon an estimate of the number of patients eligible for therapy with Fentora, the non-cancer population is approximately one order of magnitude higher than the cancer population.

Our estimate shows that the number of patients eligible for Fentora is approximately ten times the number eligible with the currently approved indication.

ABBREVIATIONS

AE	Adverse Event
ATC	Around-the-clock
BTP	Breakthrough pain
SAE	Serious Adverse Event
SPA	Special Protocol Assessment

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Joint Meeting of the
Anesthetic and Life Support Drugs Advisory Committee
and
Drug Safety & Risk Management Advisory Committee
Discussions Points for the Committee
Fentora AC Meeting
May 6, 2008

1. Based on the differences in breakthrough pain in patients with and without cancer, discuss whether you believe there is a need to expand the indication for this product from the treatment of breakthrough pain in opioid-tolerant cancer patients to the treatment of breakthrough pain in opioid-tolerant non-cancer patients

2. Given the discrepancy in the adverse event profile for certain events between the cancer and non-cancer population and the fatalities observed in postmarketing surveillance, discuss whether it is feasible to expect Fentora will be safely used in the proposed population.

3. In light of the increasing abuse of prescription opioids in general, and the specific attributes of this product which make it particularly attractive for abuse, are you concerned that increased prescribing may lead to increased diversion and abuse?

    a. Discuss how this risk could be mitigated without preventing access to legitimate patients.

4. Do you believe the risks of abuse, misuse and diversion can be managed or minimized?

    a. Please discuss the benefit to pain patients included in new indications compared to the potential public health consequences if widespread diversion and abuse occur

5. Do you believe the new expanded indication for the management of breakthrough pain in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain should be approved?

    a. If yes, which specific aspects of risk management should be incorporated into the approval plan for this application?

    b. If no, is there further development that the sponsor could perform to lead to approval of this indication?