FENTORA® (fentanyl buccal tablet) CII

United States Food and Drug Administration

Joint Meeting

Anesthetic and Life Support Drugs Advisory Committee
and

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
Abuse	The term abuse is used in this document to refer to any component of the disease of addiction (as defined below).
Addiction	Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (Savage et al 2003).
Dependence	The term dependence is used in this document interchangeably with the terms abuse and addiction. This is due to the structure of the Medical Dictionary for Regulatory Activities (MedDRA) (version 8.1) used to code adverse events, which requires that adverse events of drug abuse or drug addiction be coded to the term drug dependence. The term dependence is not used in this document to refer to physical dependence or drug withdrawal syndrome.
Diversion	The willful transfer of a drug from legitimate supply (manufacture, distribution, or storage in hospitals, pharmacies, prescribers' offices) and/or patients for whom the drug has been prescribed to unauthorized users and/or for illegal sale.
Overdose	Involves the ingestion of more than the normal or recommended amount of a substance, usually a drug. The term overdose may also be used to refer to severe signs or symptoms of drug toxicity when the actual amount of drug ingested is unknown. A drug overdose may have serious consequences, including death, and may be the result of accidental or intentional exposures to a drug.
Tolerance	Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of 1 or more of the drug's effects over time (Savage et al 2003).

Abbreviation	Term
ADR	adverse drug reaction
ATC	around the clock
AAPCC	American Association of Poison Control Centers
ACCME	Accreditation Council for Continuing Medical Education
AHFS	American Hospital Formulary Service
ASCVD	Arteriosclerotic cardiovascular disease
AUC	area under the curve
BMI	body mass index
bpm	beats per minute
BTP	breakthrough pain
CFR	Code of Federal Regulations (United States)
CHF	Congestive heart failure
CI	confidence interval
C_{max}	maximum plasma concentration
CME	continuing medical education
CNS	central nervous system
COPD	Chronic obstructive pulmonary disease
CRPS	complex regional pain syndrome
CSP	Cephalon Speaker Program
CYP	cytochrome P450
DAARP	Division of Anesthesia, Analgesia, and Rheumatology
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DIC	Disseminated intravascular coagulopathy
DPN	diabetic peripheral neuropathy
ED	Emergency Department
EDV	Emergency Department visits
ESP	Emerging Solutions in Pain

Abbreviation	Term
F	female
FBT	fentanyl buccal tablet
FEBT	fentanyl effervescent buccal tablet
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FSG	FENTORA safety group
FSMB	Federation of State Medical Boards
FAQ	Frequently asked question(s)
HCP	healthcare professional
HIPAA	Health Insurance Portability & Accountability Act of 1996
hr	hour
ICSR	Individual case safety reports
IR	immediate-release
LRx	IMS Longitudinal Database
M	male
max	maximum
MCS	Medical Claims Switch
mcg	microgram
ME	medical examiner
ME/C	medical examiner/coroner
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mg	milligram
MG	Medication Guide
mL	milliliter
MSIR	morphine sulfate immediate release
N	number
NADDI	National Association of Drug Diversion Investigators

Abbreviation	**Term**
NAV	not available
NDA	New Drug Application
ng	nanogram
NIDA	National Institute on Drug Abuse
NOS	not otherwise specified
NPA	National Prescription Audit
NSDUH	National Survey on Drug Use and Health
NTA	not tabulated above
OAS	Office of Applied Studies
OTFC	Oral Transmucosal Fentanyl Citrate
PD	pharmacodynamics
PDR	Physicians' Desk Reference
PDUFA	Prescription Drug User Fee Act
PI	package insert
po	oral (per os)
prn	as needed (pro re nada)
PROTECT	Principals of Rational Opioid Therapy: Education, Communication & Translation
PVD	Peripheral vascular disease
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation System
RFID	Radio frequency identification
RiskMAP	Risk Minimization Action Plan
RMP	Risk Management Program
RMPDC	Rocky Mountain Poison and Drug Center
RSD	Reflex sympathetic dystrophy
Rx	pharmacy
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	standard deviation

Abbreviation	**Term**
SEM	standard error of the mean
sl	sublingual
sNDA	supplemental NDA
SPID	summed pain intensity differences
$SPID_{60}$	summed pain intensity difference through 60 minutes
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	terminal half-life
TESS	Toxic Exposure Surveillance System
TIA	Transient ischemic attack
t_{max}	Time to occurrence of maximum concentration
URDD	unique recipient of dispensed drug
US	United States
USPI	Unites States package insert
y	year

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EXECUTIVE SUMMARY

Introduction

FENTORA® (fentanyl buccal tablet) is a formulation of fentanyl citrate that utilizes ORAVESCENT® technology to facilitate and enhance the absorption of fentanyl through the oral mucosa. FENTORA was approved in September 2006 by the United States (US) Food and Drug Administration (FDA) for the management of breakthrough pain (BTP) in patients with cancer who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain. FENTORA is commercially marketed under a Risk Minimization Action Plan (RiskMAP) through which strategies and tools have been implemented to minimize the following risks: use in opioid-nontolerant patients; unintended exposure; and abuse, misuse, and diversion.

Cephalon is now seeking to expand the indication for FENTORA beyond patients with cancer-related BTP to the management of BTP in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent chronic pain. Cephalon has conducted a development program in opioid-tolerant patients with chronic noncancer-related BTP to achieve approval for this expanded indication. The program was conducted in accordance with advice and guidance from the FDA. This briefing document is intended to provide the background information and rationale supporting the development of FENTORA for the expanded indication described above, to provide brief summaries of results of completed studies, to provide postmarketing findings for FENTORA, and to discuss the proposed RiskMAP.

Intended Population and Medical Need

The patients for whom FENTORA is intended represent a small proportion of the chronic pain population. Patients for whom FENTORA use would be appropriate include all of the following:

- those who have had a chronic painful condition for at least 3 months (in most cases this will be years)
- those who have painful conditions not effectively managed by nonopioid pain medications (eg, nonsteroidal anti-inflammatory medications, acetaminophen) or by short-acting oral opioids given on an as needed basis
- those who require an opioid be given around-the-clock (ATC) to manage their chronic pain
- those using a daily dose of ATC opioid of at least 60 mg of oral morphine or equivalent
- those experiencing BTP (a transient flare of moderate to severe pain) requiring intervention with additional opioid medication

Although the intended population represents a small proportion of the chronic pain population, the impact of BTP on quality of life and function can be significant. Much of the literature on BTP is focused on patients with cancer; however, authors of recent publications have characterized BTP in patients suffering from other chronic painful conditions. The characteristics of BTP are similar across painful conditions (ie, severe levels of pain intensity, maximum intensity reached within minutes of onset, multiple episodes occurring daily). Among the patients with noncancer-related BTP, there is general dissatisfaction with the most commonly used treatments (ie, short-acting oral opioids) because of their inadequate onset of effect. It is also known that substantial use of FENTORA, and its predecessor ACTIQ®, has been in the management of BTP in opioid-tolerant patients with chronic noncancer pain. Taken together, these data point to the need for a medication for the effective treatment of patients with these painful conditions having an approved indication to do so.

More information on the intended population and medical need is provided in section 2 of this document.

Background on FENTORA

FENTORA was designed to deliver fentanyl across the oral mucosa in a manner more efficient than that of ACTIQ, a fentanyl-containing medication approved for use in the management of BTP in opioid-tolerant patients with cancer.

Human pharmacokinetic studies have shown that the bioavailability of fentanyl from FENTORA (65%) is higher than that of ACTIQ (50%) and the peak plasma concentrations are achieved in half the time. This occurs because a larger portion of the FENTORA dose (50%) is absorbed across the oral mucosa compared with the ACTIQ dose (25%). These characteristics produce a pharmacokinetic profile that more closely matches the onset characteristics (ie, rapid increase in pain intensity) of BTP.

More information on the background of FENTORA is provided in section 3 of this document.

FENTORA Clinical Program in Opioid-Tolerant Patients With Noncancer-Related Pain and Breakthrough Pain

It was discovered during postmarketing experience with ACTIQ that there was use of this product in opioid-tolerant patients with noncancer-related BTP, indicating a medical need in this population of patients. A clinical program evaluating FENTORA in this population was, therefore, undertaken early in the product's development. The ensuing clinical program was the first of its kind. The size and design of the program was determined with input from the FDA.

ACTIQ is a registered trademark of Anesta Corp., a wholly owned subsidiary of Cephalon, Inc.

Included in the supplemental NDA submission were 4 Phase 3 studies: 3 safety and efficacy studies and one 18-month open-label safety study. All patients who entered these studies were to be taking at least 60 mg of oral morphine or equivalent for the management of their persistent pain and treating at least 1-4 BTP episodes per day with a short acting opioid.

More information on the FENTORA clinical program is provided in section 4.1 of this document.

Patient Population

There were 941 patients enrolled in these clinical studies. The average age of the patients was 48.7 years and the majority (57%) were women. The chronic painful conditions of the patients were typical of the general chronic pain population requiring ATC opioid therapy. The most common conditions represented included back pain (55%), neuropathic pain from a traumatic injury (10%), complex regional pain syndrome (6%), and osteoarthritis (6%). Patients were required to be using at least 60 mg of oral morphine (or equivalent) as their ATC medication; however, at study entry, the majority of patients were taking substantially more than this minimum dose, as the median dose was 160 mg/day.

Patients in these studies had multiple comorbid conditions and were generally using multiple concomitant medications. Consistent with an opioid tolerant population of patients with moderate to severe chronic noncancer-related pain, 77% had a history of neurologic abnormalities and 73% had a history of psychiatric abnormalities. Of note, high rates of abnormal medical history were also seen in the cardiovascular (58%), respiratory (40%), and endocrine (35%) systems, consistent with a high rate of comorbid medical conditions such as hypertension, chronic obstructive pulmonary disease, and diabetes. More than 99% of patients were receiving medications at baseline in addition to their analgesic medications.

More information regarding the population of patients included in the clinical studies is provided in section 4.2 of this document.

Efficacy

Of the 3 efficacy studies conducted, 1 was pivotal and 2 were supportive. All 3 studies had similar designs. All began with patients titrating FENTORA to a dose between 100 and 800 mcg found to be effective and tolerable. Efficacy was assessed using a within-patient design (ie, patient served as their own control). The pivotal study was designed in collaboration with the FDA and assessed efficacy over a 12-week treatment period. In this study, patients used study drug for their episodes of BTP daily for 12 weeks following titration; efficacy was assessed in a double-blind fashion every 4 weeks. The primary time point of interest was week 12.

All 3 efficacy studies demonstrated consistent results with statistically significant and clinically relevant improvements in pain intensity and pain relief in favor of FENTORA as compared with placebo. The pattern of effect across measures showed that analgesic

activity with FENTORA could be detected early after initiating treatment, often by 10 minutes, and the effect was maintained throughout the 2-hour observation period. The clinically relevant improvements observed were based both on well established cut-off points in pain intensity changes (≥33% and ≥50% improvement) and from patient reports of meaningful pain relief.

More information regarding efficacy data is provided in section 4.3 of this document.

Safety

The clinical program in noncancer-related BTP included 941 patients, representing 227,047 patient-treatment days of exposure. A total of 319 patients were treated for more than 1 year. The most common adverse events observed in the clinical studies included nausea, vomiting, constipation, dizziness, and somnolence, all of which are commonly seen with opioid treatment. A total of 7 deaths occurred, 6 of which occurred in patients participating in a long-term safety study, all with causes likely associated with pre-existing diseases. Thus, none were considered related to treatment with study drug. Despite the controlled setting of the clinical studies, 1 person not participating in a study experienced a fatal overdose after diverting study drug from his wife, who was a study participant. For further details on deaths, see section 4.4.3.2.

In the clinical studies, 14% of patients had serious adverse events, most of which were attributable to co-existent medical conditions, with no specific pattern identified. A total of 10 cases of overdose were observed in clinical study patients, none of which were fatal. Discernible causal factors for overdose included suicide attempt, polysubstance abuse, and the availability of multiple dose strengths during the titration periods. In some patients, the circumstances were not known. The proposed RiskMAP (as outlined in section 6) addresses these and other reasons for overdose.

In the FENTORA chronic noncancer pain program, 8 patients had events consistent with drug abuse and 13 patients had positive urine drug screen results for illicit substances or nonprescribed drugs. Recognizing that drug abuse is an area of concern with regard to opioids, a post hoc analysis of the occurrence of aberrant behaviors was performed by applying criteria and definitions commonly used in the clinical practice setting to identify any reports possibly consistent with aberrant behavior. Results showed that patients 42 years of age or younger and patients with a medical history suggestive of mania or psychosis had a greater probability of displaying aberrant behavior. Aberrant behavior and its risk factors are specifically addressed in the RiskMAP (see section 6).

The safety and tolerability observed in the clinical program is consistent with the known safety profile of fentanyl and the population studied. Overall there were no unexpected findings with FENTORA treatment.

More information regarding safety data is provided in section 4.4 of this document.

Postmarketing Safety Findings

Post-marketing data are based on the cumulative observations over the 15 months from the launch of FENTORA through the end of 2007. During this time frame, more than 2 million patient-treatment days of exposure experience has been accumulated.

The postmarketing safety profile of the most frequently voluntarily reported adverse events is as expected with fentanyl.

There were a total of 5 postmarketing fatalities and 1 life-threatening event in patients prescribed FENTORA. Two of the fatalities were related to progression of cancer. Three events occurred in patients for whom FENTORA was prescribed for migraine or headache, patients with these painful conditions are generally considered opioid nontolerant. These fatalities occurred within a relatively narrow time frame during the summer of 2007 and triggered immediate and long-term interventions to prevent further occurrences (see section 6.1.2).

Two cases of diversion and 3 cases of misuse or abuse were reported. In both cases of diversion, the partner of a clinical study patient diverted FENTORA and experienced a fatal overdose (see section 4.4.6).

During the postmarketing observation period, 26 reports of medication errors were received. Reasons included errors in dose conversion from ACTIQ, sublingual rather than buccal administration (data now available showing the 2 routes bioequivalent), and too frequent use of FENTORA. These causes, particularly the dose conversion errors and schedule of use, are specifically addressed in the RiskMAP.

Overall, the observed postmarketing safety and tolerability data are consistent with the safety and tolerability observed in the clinical study program. This is also consistent with what would be expected from a fentanyl-containing drug formulation. There were no unexpected findings during the postmarketing observation period.

More information regarding postmarketing data is provided in section 5 of this document.

Risk Management for FENTORA

Cephalon has accumulated considerable experience over the past decade in risk management. The experience began with the approval of ACTIQ, which was the first schedule II opioid analgesic product introduced with a risk management plan, and continued with a RiskMAP with the introduction of FENTORA for the indication of cancer-related BTP. For the expanded indication sought (ie, management of BTP in opioid-tolerant patients with noncancer-related BTP), Cephalon has proposed enhancements to the currently used RiskMAP.

The development of the RiskMAP has followed FDA guidance with emphasis placed on an iterative process of implementation, evaluation, reassessment, and adjustment of tools to minimize the risks while preserving the benefits of FENTORA. Through the use of a failure mode effects analysis, a prospective risk management assessment, Cephalon has

identified the following 2 primary risks that require mitigation with the use of FENTORA:

- risk of FENTORA overdose
- risk of abuse and diversion

For both risks, respective goals and objectives were identified to prevent their occurrence.

The product distribution cycle was evaluated to determine points where the 2 identified risks could be addressed. The following 6 points of possible intervention were identified: supply chain, point of prescribing, point of dispensing, point of consumer storage, point of patient use, and disposal of the product. These points of intervention were then assessed to evaluate their possible impact on the identified risks, and the impact on each of the target audiences: prescriber, pharmacist, and patient (and/or caregiver).

This structured approach allowed for the careful selection of appropriate tools targeted at the points of intervention to minimize the risks.

Of the approximately 800,000 prescribers with a Drug Enforcement Administration (DEA) registration to prescribe schedule II drugs in the US, Cephalon will target 4% to receive information about FENTORA. These are the same prescribers currently reached. These individuals represent the most skilled prescribers of schedule II opioids.

The second key strategy is the dissemination of key messages about FENTORA and its associated risks. These will be conveyed via tools tailored to specifically address points of intervention and to fit each of the target audiences. For each of the points of intervention, multiple tools have been selected to deliver key safety messages to cover the different target audiences and to cover the different learning strategies of the target audiences such as computer-based initiatives, in-person communications, print communications, and continuing education and distance learning initiatives.

In order to measure the effectiveness of the tools utilized, specific surveillance systems have been employed, as follow:

- RADARS® and DAWN Live! (Researched Abuse, Diversion and Addiction-Related Surveillance and Drug Abuse Warning Network)
- American Association of Poison Control Centers
- media monitoring
- Cephalon pharmacovigilance system
- survey data obtained with target audiences: patients, prescribers, and pharmacists
- review of prescribing data, such as IMS prescription data

The benefit-risk balance for FENTORA is constantly reassessed, on the basis of data received through the surveillance tools, by the FENTORA safety group, the Cephalon Corporate Safety Board, and the external RiskMAP Advisory Board. All surveillance data and Cephalon considerations are provided to the FDA on a quarterly basis, and there is ongoing dialogue with the FDA. To assess whether specific tools need to be adjusted,

or if new tools need to be added, Cephalon has developed an algorithm that utilizes various information and identifies targeted interventions.

More information regarding the FENTORA RiskMAP is provided in section 6 and regarding findings derived from the current RiskMAP in cancer BTP in sections 5.8 and 5.9.

Benefit/Risk Profile of FENTORA

There is a need to manage BTP in opioid-tolerant patients with chronic pain regardless of whether the pain is a result of cancer or another chronic condition. The efficacy of FENTORA treatment in this population has now been demonstrated with the results from this the first-of-its-kind clinical study program. The safety risks associated with FENTORA are known and common to potent opioids.

Cephalon has instituted a RiskMAP for FENTORA that incorporates specific educational and active interventions to mitigate against overdose, abuse, and diversion. The intentional duplication of messaging and built-in redundancies accommodate all major modalities of educational activities for the target audiences. Cephalon views the FENTORA risk management program as an iterative process for the life of the product—a continuous cycle of interventions, metrics, assessments, and adjustments. Cephalon commits to adapt and incorporate any necessary modifications as data accumulate and knowledge increases, just as it has demonstrated in the past.

It is through the implementation of this RiskMAP that the benefits of FENTORA can be realized by patients in need, while keeping the main risks associated with this product at an acceptable level.

1 INTRODUCTION

FENTORA® (a fentanyl-containing tablet for buccal administration[1]) is currently approved in the United States (US) for the management of breakthrough pain (BTP) in patients with cancer who are opioid tolerant, ie, who are already receiving and who are tolerant to around-the-clock (ATC) opioid therapy for their underlying persistent cancer pain.

Many patients with chronic pain from sources other than cancer experience BTP, a transient flare of moderate to severe pain. Through a supplemental New Drug Application (sNDA), Cephalon is seeking an expanded indication for the use of FENTORA for the management of BTP in opioid-tolerant patients.

This briefing document provides details on the prevalence and the need to manage BTP in patients with noncancer-related chronic pain, FENTORA ORAVESCENT® formulation technology and human pharmacokinetics, clinical and regulatory background on the FENTORA clinical program in opioid-tolerant patients with noncancer-related BTP, and efficacy and safety data from the clinical program. Postmarketing data for FENTORA from the Cephalon pharmacovigilance system are provided, Cephalon's experience in risk management is summarized, and enhancements to the current FENTORA Risk Minimization Action Plan (RiskMAP) for the expanded indication are detailed and explained. Finally, detailed information about the proposed Cephalon RiskMAP in the context of the expanded indication is provided, specifically product risks and risk minimization goals, tools for intervention, surveillance systems and monitoring activities, and safety signal detection and evaluation.

[1] Fentanyl is listed in Schedule II of the United States (US) Food and Drug Administration (FDA) Controlled Substances Act.

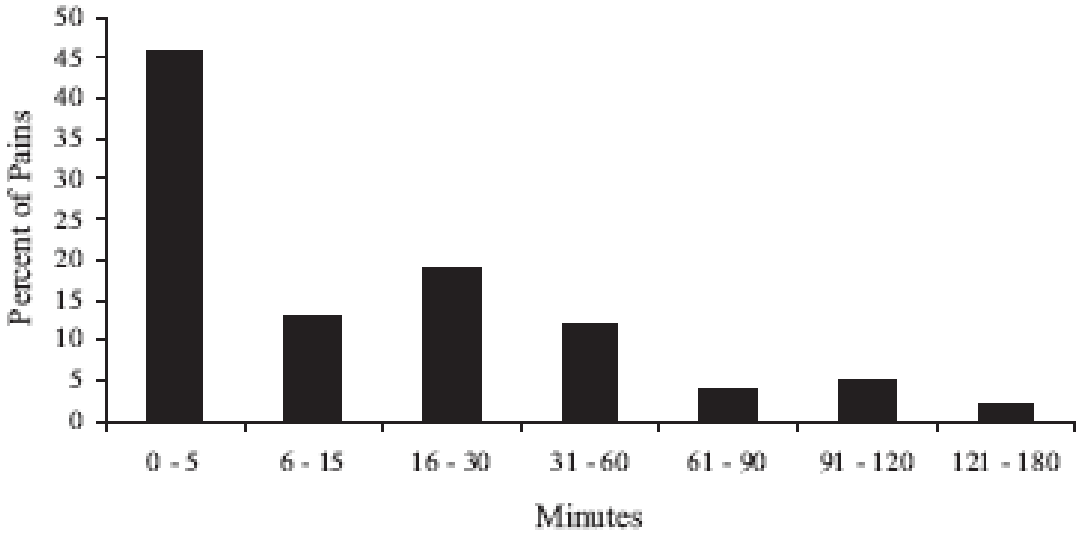
2 NEED FOR THE MANAGEMENT OF BREAKTHROUGH PAIN IN NONCANER-RELATED CHRONIC PAIN CONDITIONS

Chronic pain, a common cause of major disability, is estimated to affect as many as 1 in 5 adult Americans. Inadequate pain control has profound consequences, such as psychological morbidity (including anxiety and depression) and significant functional impairment (Gureje 1998). Inadequate treatment also leads to increased direct and indirect healthcare costs. Over the past 20 years, there has been a greater effort on the part of the medical community to actively identify patients with painful conditions to adequately treat patients with pain. For patients for whom treatment with standard analgesics is ineffective in providing adequate pain control, opioids are the therapy of choice (Dworkin et al 2003, World Health Organization Expert Committee 1990, World Health Organization 1996). For patients with more severe chronic persistent pain, ATC opioid therapy is indicated, with longer-acting formulations often being the treatments of choice (Dworkin et al 2007, Chou and Huffman 2007, Chou et al 2007). ATC opioid therapy can be effective in controlling the level of persistent pain; however, patients with chronic pain often still experience transient exacerbations of pain referred to as breakthrough pain (BTP).

Much of the medical literature surrounding BTP originates from studies of patients with cancer-related pain. In these patients, BTP has been characterized as rapidly escalating flares of pain, often reaching peak intensity within 3 minutes, having a median duration of 30 minutes (Portenoy 1990). While patients can sometimes identify a precipitant that causes BTP, such as movement or cold weather, most patients report that the onset of BTP is unpredictable. BTP occurs despite appropriate treatment with ATC analgesic medications, and is associated with relatively more severe levels of chronic persistent pain. BTP also results in worsening of pain-related interference in sleep, walking, daily activities, enjoyment of life, and relationship with others. Compared to patients with other chronic pain conditions, patients with BTP have higher rates of anxiety and depression (Portenoy et al 1999).

Portenoy et al (2006) reported results of a survey undertaken regarding the prevalence and characteristics of BTP in opioid-tolerant patients with chronic noncancer-related pain. Of the 228 patients with controlled chronic pain who were surveyed, 168 (74%) reported BTP, with a median of 2 BTP episodes per day. Similar to BTP episodes experienced by patients with cancer, patients with chronic noncancer-related pain reported episodes of rapidly escalating pain intensity with an onset that was most often unpredictable. The median time to peak intensity was 10 minutes; maximal pain intensity was reached within 5 minutes for 48% of episodes and within 30 minutes for 78% of episodes (Figure 2-1). The median duration of BTP episodes was 60 minutes. The survey population of patients with noncancer-related BTP was mostly white (92%), female (58%), and less than 50 years of age (56%). The most common chronic pain syndromes were low back pain (52%), neuropathic pain (11%-18%), and complex region pain syndrome (8%).

Figure 2-1: Onset of Breakthrough Pain: Time to Maximal Intensity



N=189 breakthrough pain episodes.
Portenoy 1999.

BTP should be assessed and managed independently of background chronic pain (Bennett et al 2005a, Bennett et al 2005b), as part of an overall pain management program. Thus, BTP is a major component of a public health concern regarding the undertreatment of patients with pain, which has become a national quality-of-care issue and a priority concern of the Agency for Healthcare Research and Quality (2008). BTP remains inadequately managed in the chronic noncancer pain population, and as such, a therapy that effectively manages these BTP episodes and has an acceptable tolerability profile is needed.

An initial strategy for managing BTP in patients with chronic pain who are taking ATC opioids may involve adjustment of the amount or type of ATC medication. While this may be effective in reducing the overall frequency of BTP episodes, increasing the dose of a long-acting opioid increases the risk of side effects such as sedation, and does not altogether prevent the emergence of BTP (Bennet et al 2005b). The more common practice for managing BTP incorporates supplemental treatment with short-acting analgesics despite these not having been evaluated in clinical studies. The most regularly used medications for BTP are immediate-release (IR) formulations (tablets, capsules, or liquid concentrates) of oral opioids such as morphine, hydrocodone, hydromorphone, and oxycodone. These medications, however, typically require 30 minutes or more to begin to take effect (Bennett et al 2005, Christie et al 1998, Cleary 1997, Portenoy et al 1999). In the survey conducted by Portenoy et al (2006) in which most patients were using short-acting opioids for BTP, 65% of patients reported that their BTP did not respond consistently to the interventions used.

ACTIQ® (oral transmucosal fentanyl citrate, a lozenge on a handle) was the first medication granted FDA approval for the management of BTP in patients with cancer who are already receiving, and who are tolerant to, ATC opioid therapy for their underlying persistent cancer-related pain. ACTIQ was launched in the US in April 1999 under a risk management plan (RMP) consistent with the approved indication for its use for managing BTP in patients with cancer. Despite this restriction, much of the use of ACTIQ is in noncancer-related BTP, thus endorsing the notion that BTP in the noncancer population occurs and these patients are seeking effective treatment. Therefore, Cephalon recognized the need to evaluate FENTORA for the management of BTP in both the cancer and noncancer chronic pain populations. To date, no medication has been systematically evaluated in clinical studies or approved by the FDA for the management of BTP in patients with chronic persistent noncancer-related pain.

FENTORA, a buccal tablet, is currently indicated for cancer-related BTP and has been extensively studied in Phase 3 clinical studies for the management of BTP in opioid-tolerant patients with noncancer-related BTP. The information in this briefing document will illustrate that FENTORA is well suited for the management of BTP in these patients because its analgesic profile more closely approximates the onset of a BTP episode, and the benefits of the product outweigh its risks.

3 BACKGROUND ON FENTORA

3.1 History of Fentanyl as Treatment for Patients With Chronic Pain and Breakthrough Pain

First synthesized in the late 1950s, fentanyl citrate is a potent opioid agonist acting primarily through interaction with μ receptors located in the brain, spinal cord, and smooth muscle. The most clinically useful pharmacologic effects of the interaction of fentanyl with μ receptors are analgesia and sedation. Fentanyl has a profile of pharmacologic activity similar to that of morphine, but with greater potency and a shorter duration of action.

Fentanyl was introduced into medical practice in the 1960s as an intravenous anesthetic under the trade name of SUBLIMAZE® (Janssen Pharmaceutica). The primary medical uses of fentanyl are as an intravenous analgesic, a sedative, an anesthetic before and during surgery and for postoperative pain, an analgesic for chronic pain (transdermal patch preparation), and an analgesic for BTP in opioid-tolerant patients with cancer (ACTIQ and FENTORA).

Fentanyl has been extensively used as an analgesic for chronic pain. DURAGESIC® (fentanyl transdermal system, Ortho-McNeil, Inc.), a fentanyl transdermal patch used in chronic pain management, was approved in 1990. DURAGESIC is indicated for the management of persistent, moderate to severe chronic pain that requires continuous ATC opioid administration for an extended period of time and cannot be managed by other means such as nonsteroidal analgesics, opioid combination products, or immediate-release opioids. DURAGESIC use is limited to those patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose equivalent to at least 25 mcg/hour of DURAGESIC.

Cephalon has extensive experience with the development and marketing of fentanyl products. ACTIQ, a fentanyl-containing lozenge on a handle, was approved in the US in November 1998 and launched for US marketing in April 1999 for the management of BTP in patients with cancer who are already receiving and are tolerant to opioid therapy. FENTORA, a fentanyl-containing buccal tablet, was approved in the US in September 2006 and launched for US marketing in October 2006 for the management of BTP in opioid-tolerant patients with cancer. In November 2007, Cephalon submitted a supplemental NDA for the use of FENTORA in opioid-tolerant patients with chronic pain and BTP.

3.2 FENTORA Technology and Human Pharmacokinetics

3.2.1 Development of ORAVESCENT® Technology

FENTORA is a novel formulation of fentanyl that utilizes proprietary technology to facilitate delivery and enhanced absorption of fentanyl through the oral mucosa to produce its analgesic effect (Pather et al 2001). FENTORA employs the ORAVESCENT drug delivery technology, which generates a chemical reaction that releases carbon

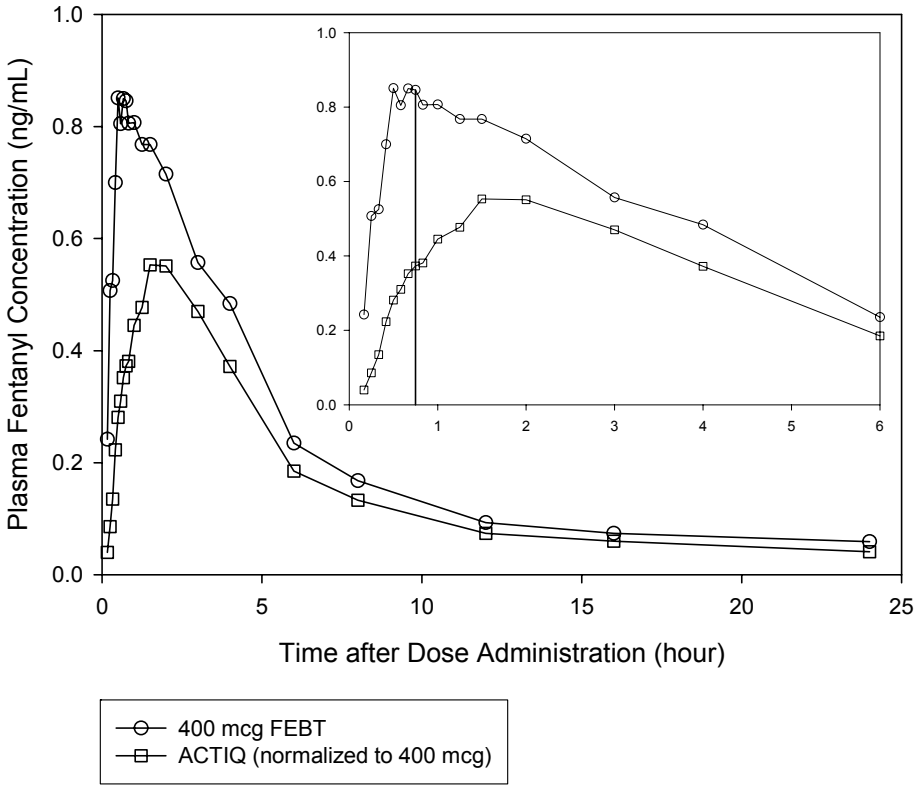
dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction optimizes dissolution and membrane permeation of fentanyl through the buccal mucosa.

3.2.2 Human Pharmacokinetics

This summary of human pharmacokinetics focuses on clinical pharmacology data from studies designed to characterize the formulation-dependent aspects of the pharmacokinetics of fentanyl from FENTORA.

The absorption profile of fentanyl from FENTORA is largely the result of an initial rapid absorption from the buccal mucosa, with peak plasma concentration (C_{max}) attained at approximately 50 minutes. Peak concentration of fentanyl in the arterial circulation is approximately 60% higher and occurs 15 minutes earlier than measured from the venous circulation. Approximately 50% of the total dose administered is absorbed across the buccal mucosa and rapidly becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract. In comparison, the fraction of the ACTIQ dose absorbed transmucosally is approximately 25% of the total dose. As a result, FENTORA demonstrates a higher absolute bioavailability (65%) when compared with ACTIQ (50%). The differences in absolute bioavailability and in the fractions absorbed transmucosally between FENTORA and ACTIQ must be taken into consideration when selecting dose regimens or switching treatment regimens (Figure 3-1).

Figure 3-1: Mean Plasma Concentration Versus Time Profiles Following Single Doses of FENTORA (400 mcg) and ACTIQ (Dose Normalized to 400 mcg) in Healthy Subjects



NOTES: Inset shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the $t_{max'}$. FENTORA is also referred to as FEBT (fentanyl effervescent buccal tablet). $t_{max'}$=time to maximum plasma concentration (t_{max}) for the reference treatment.

The FENTORA pharmacokinetic profile demonstrates that, within 25 minutes, fentanyl concentrations reach approximately 80% of C_{max} and are maintained through approximately 2 hours. Concentrations decline following 2 hours after the start of administration with an effective half-life ($t_{½}$) of approximately 4 hours. Following repeat dose administration of FENTORA every 4 to 6 hours, fentanyl concentrations are approximately 2 times those observed with the first dose.

The rate and extent of fentanyl absorption following administration of FENTORA are not affected by the length of time between tablet placement and the complete disappearance of tablet residue from the oral cavity (the dwell time). Furthermore, plasma exposure following sublingual placement of FENTORA is equivalent to that observed following buccal placement.

As presented above, the formulation-dependent aspects of the pharmacokinetics of FENTORA produce desirable plasma concentrations with lower doses of fentanyl than those in ACTIQ. Furthermore, this pharmacokinetic profile more closely approximates the time profile of a BTP episode (ie, rapid increase in associated pain intensity).

4 FENTORA CLINICAL PROGRAM IN OPIOID-TOLERANT PATIENTS WITH NONCANCER-RELATED PAIN AND BREAKTHROUGH PAIN

4.1 Regulatory Background, Clinical Program Rationale, and Description of Clinical Studies

4.1.1 Regulatory Background

ACTIQ was approved in the US in November 1998 under a risk management plan, and launched for US marketing in April 1999 for the management of BTP in patients with cancer who are already receiving and are tolerant to opioid therapy. FENTORA was approved on 25 September 2006 for the management of BTP in opioid-tolerant patients with cancer. An sNDA was submitted on 9 November 2007 supporting the use of FENTORA for the management of breakthrough pain in opioid-tolerant patients with chronic pain.

The clinical development of FENTORA for use in opioid-tolerant patients with chronic pain began in 2005 with the initiation of a long-term open-label safety study (study 3040). In a teleconference with the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) on 12 October 2005 and subsequent written correspondence from the FDA on 8 November 2005, the FDA indicated the requirements for the approvability of an expanded indication for the use of FENTORA in opioid-tolerant patients with chronic noncancer pain and BTP as follows: one clinical study designed to evaluate efficacy after 12 weeks of treatment ensuring that patients enrolled had a diverse range of painful conditions (no more than 60% could have low back pain, the remaining 40% having other types of pain), and the safety database would need to be in excess of 1000 patients, the majority of whom would have pain due to noncancer etiologies; 300-500 patients would have to be treated for at least 6 months and 100 patients for at least 1 year.

General agreement was reached upon the study design and study 3052 was initiated in August 2006. Cephalon submitted the statistical analysis plan in support of study 3052 on 16 November 2006 and received comments from FDA in a letter of 3 April 2007. The statistical analysis plan was revised to incorporate FDA recommendations.

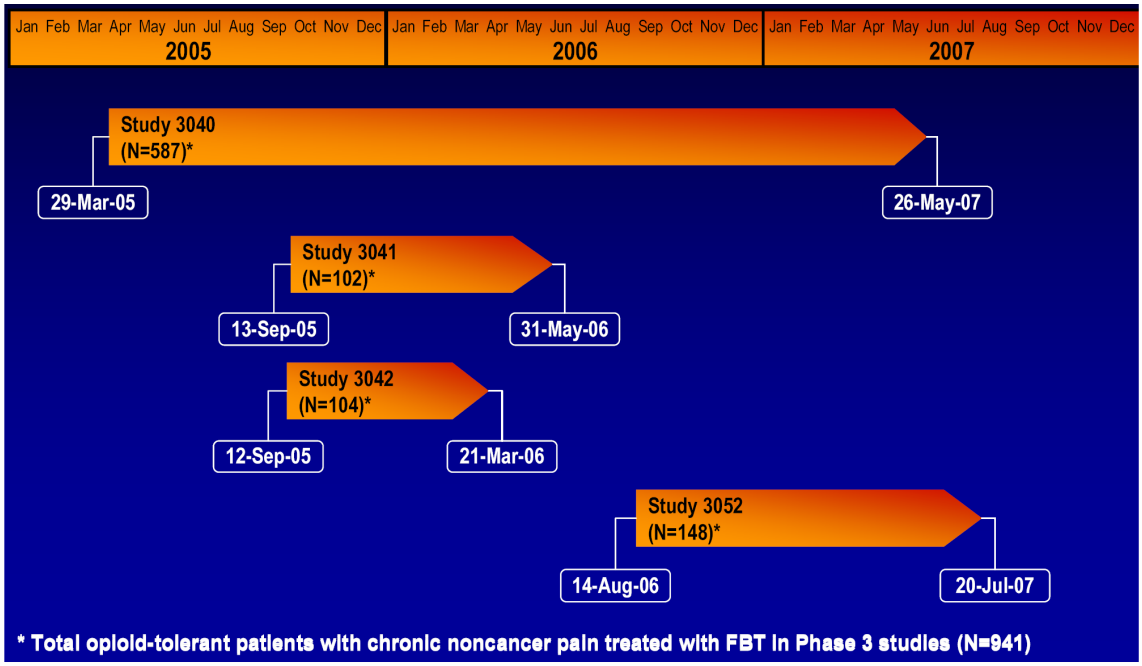
4.1.2 Clinical Program Rationale

The clinical program for FENTORA in opioid-tolerant patients with noncancer-related persistent pain and BTP was developed on the basis of the following considerations:

- the well-characterized profile of fentanyl as an opioid analgesic used in clinical practice for over 40 years
- experience in developing ACTIQ and FENTORA for treatment of patients with cancer-related BTP
- knowledge that ACTIQ was also being used for the management of BTP in patients with chronic noncancer-related pain

The clinical trial program for FENTORA for the expanded indication began with a long-term open-label study and continued with 3 subsequent efficacy studies with similar key design features (Figure 4-1).

Figure 4-1: FENTORA Clinical Program Timeline for Noncancer-Related Breakthrough Pain and Numbers of Patients



FENTORA is also referred to as FBT (fentanyl buccal tablet).

In September 2005, 2 double-blind efficacy studies in opioid-tolerant patients with chronic noncancer-related pain and BTP (studies 3041 and 3042) were initiated. These 2 studies were similar in design to the pivotal study conducted in opioid-tolerant patients with cancer and BTP submitted with the initial NDA. Study 3041 included opioid-tolerant patients with chronic neuropathic pain and BTP, and study 3042 included opioid-tolerant patients with chronic low back pain and BTP.

Patients with chronic noncancer-related BTP would be expected to use a medication like FENTORA for longer periods of time than if they had cancer; therefore, in collaboration with the FDA Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), Cephalon designed the pivotal study for the expanded indication (study 3052). This study was designed to assess the efficacy of FENTORA over 12 weeks (after titration), with the primary time point of interest being at the end of 12 weeks. Study 3052 was initiated in August 2006 and completed in July 2007.

4.1.3 Description of Clinical Studies of Patients With Noncancer-Related Breakthrough Pain

The 3 efficacy studies (pivotal study 3052 and supportive studies 3041 and 3042) had similar patient populations, within-patient study designs, and outcome measures.

The studies included opioid-tolerant patients, 18 years or older, with chronic noncancer-related pain (at least 3 months duration) and BTP. All patients were taking ATC opioids for their underlying chronic painful condition and experiencing 1-4 BTP episodes per day having average pain intensity less than 7 over prior 24 hours. Patients in study 3052 had various chronic pain diagnoses, in study 3041 they had neuropathic pain, and in study 3042 they had low back pain. Patients were considered opioid tolerant if they were already receiving at least 60 mg of oral morphine/day, 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 for a week or longer for their chronic persistent pain.

In all studies study drug was individually titrated for each patient to a successful dose (ie, a dose of FENTORA that provided adequate analgesia without unacceptable adverse events). Efficacy assessments were made during randomized, double-blind, placebo-controlled, with-in patient treatment periods in which study drug was used for 9 BTP episodes (6 FENTORA and 3 placebo). Study 3052 had 3 of these double-blind periods (weeks 4, 8, and 12), whereas studies 3041 and 3042 each had 1 double-blind period. With this within-patient design, patients served as their own controls. The fourth study was an 18-month open-label safety study.

The clinical program for FENTORA in noncancer-related BTP included patients with a variety of chronic painful conditions (Table 4-1).

Table 4-1: Chronic Painful Conditions in Phase 3 Studies in Patients With Chronic Noncancer-Related Pain and Breakthrough Pain

Study 3052	Study 3041	Study 3042	Study 3040 (new patients only)
Chronic pain associated with DPN, postherpetic neuralgia, traumatic injury, CRPS, back pain, neck pain, fibromyalgia, chronic pancreatitis, or osteoarthritis.	Chronic neuropathic pain associated with DPN, postherpetic neuralgia, traumatic injury, or CRPS.	Chronic low back pain associated with osteoarthritis, degenerative disk disease, or spondylolisthesis.	Chronic low back pain from osteoarthritis, degenerative disc disease, or spondylolisthesis, postherpetic neuralgia, CRPS, DPN, osteoarthritis, traumatic injury, or chronic headache.

DPN=diabetic peripheral neuropathy; CRPS=complex regional pain syndrome.
NOTE: Patients with other chronic painful conditions could be included with the approval of the Cephalon medical expert. In study 3052, the protocol set a limit of 60% on the proportion of the entering population whose primary painful condition was back pain. Patients with chronic headache were required to be receiving around-the-clock opioids and having breakthrough pain; study 3040 was the only study in which patients with headache were included.

The efficacy measures used to assess pain intensity and pain relief are well accepted and commonly used in the evaluation of pain. Pain assessments were measured from 5 through 120 minutes after each treated episode. Other efficacy assessments included patient global perspective of pain relief and use of additional rescue medication.

The primary efficacy outcome variable was the sum of the pain intensity differences (SPID) through 60 minutes ($SPID_{60}$) after administration of study drug used for an episode of BTP during double-blind treatment. The $SPID_{60}$ is a cumulative measure of pain intensity difference over a 60-minute period after drug administration, with pain intensity recorded pre- and posttreatment on a scale of 0 to 10. The $SPID_{60}$ may be likened to an area under the curve (AUC) with regard to change in pain intensity over 60 minutes—the greater the $SPID_{60}$, the greater the improvement. An additional analysis of pain intensity data was performed to calculate the percentages of episodes with at least a 33% and 50% reduction at specified time points. An improvement of 33% or greater is considered moderate improvement, with a 50% improvement considered substantial improvement (Dworkin 2008).

4.2 Patient Population in Studies of Noncancer-Related Breakthrough Pain

The 4 Phase 3 studies in the supplemental NDA included 941 patients treated with FENTORA. The 941 patients with noncancer-related BTP plus the 358 patients from the Phase 3 clinical studies of FENTORA in opioid-tolerant patients with cancer-related BTP resulted in a total of 1299 patients exposed to FENTORA in clinical studies.

Among the 941 patients in the FENTORA clinical program for chronic noncancer-related pain, the vast majority (95%) were less than 65 years old and were white (93%) (Table 4-2).

Table 4-2: Demographic Characteristics of Patients With Noncancer-Related Breakthrough Pain

Demographic characteristic	Total (N=941)
Mean age (range), years	48.7 (20-77)
<65 years	95%
≥65 years	5%
Men	43%
Women	57%
White	93%
Nonwhite	7%
Mean BMI (range), kg/m^2	30.2 (14.3-76.3)

BMI=body mass index.

The pain characteristics of the patients from the FENTORA clinical studies are similar to those found by Portenoy et al (2006) in their survey on the prevalence and characteristics of BTP in opioid-tolerant patients with chronic noncancer-related pain (Table 4-3).

Table 4-3: Pain Characteristics of Patients With Noncancer-Related Breakthrough Pain

Pain characteristic	Total (N=941)
Primary pain group, n (%)	
Back pain	518 (55)
Neuropathic pain	191 (20)
Other pain types	232 (25)
Common chronic pain condition, %	
Back pain	55
Traumatic injury	10
Complex regional pain syndrome	6
Osteoarthritis	6

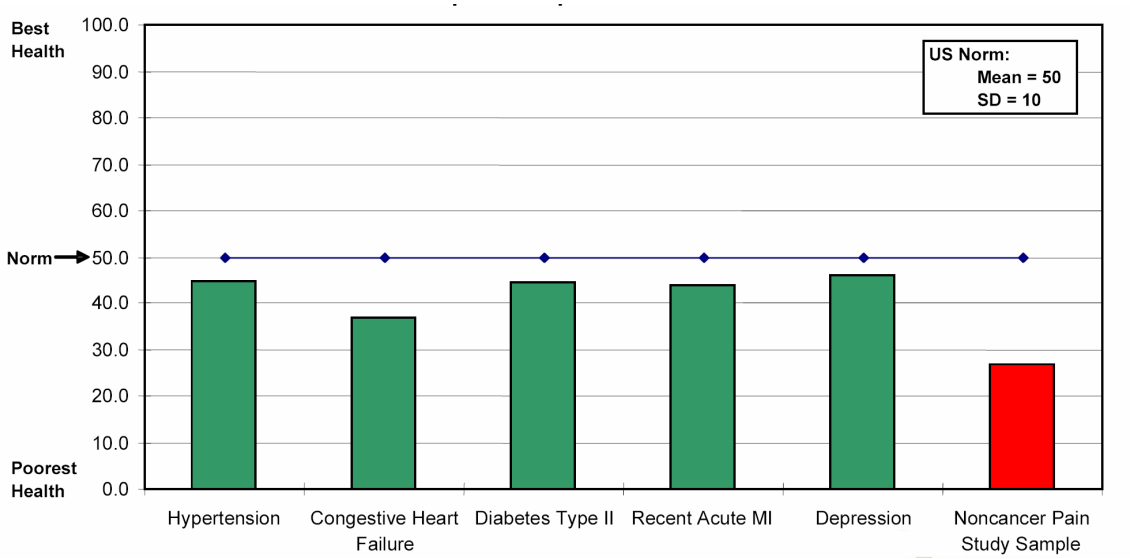
Prior to study entry, patients were asked to rate (on a scale of 0 [no pain] to 10 [the worse pain imaginable]) average pain intensity over the previous 24 hours for their chronic persistent pain. Median chronic pain intensity was 5. For the patients BTP, among the Phase 3 double-blind studies, median pretreatment pain intensity ranged from 7.0 to 7.3.

Patients in these studies had multiple comorbid conditions. All 941 (100%) patients had at least 1 abnormal finding in their medical history. The most frequent abnormalities (≥75% of patients) occurred in the musculoskeletal, neurologic, and gastrointestinal systems. The rate of abnormal medical history in the cardiovascular (58%), respiratory (40%), and endocrine (35%) systems is consistent with a high rate of comorbid medical conditions such as hypertension, chronic obstructive pulmonary disease, and diabetes in this population of patients with chronic pain.

Patients entering these studies completed a 36-Item Short Form Health Survey (SF-36). Results for Physical Health Summary score showed that patients entering these studies

were in poorer health than observed with patients with other chronic pain conditions such as congestive heart failure, diabetes, or recent myocardial infarction (Figure 4-2).

Figure 4-2: Norm-Based Scoring of SF-36 Physical Health Summary Score in Adults: Noncancer-Related Pain Compared With 5 Other Medical Conditions



SF-36=The 36-Item Short Form Health Survey; US=United States; MI=myocardial infarction.
Ware et al 1994.

In the Phase 3 studies, 98% of patients were taking medications in addition to other opioid analgesics at study entry, with 66% taking 5 or more medications. At baseline, for their ATC medication, 73% of patients were taking oral opioids, 24% of patients were using transdermal fentanyl, and 3% were using intrathecal medications (Table 4-4). The doses of these medications were often substantially higher then the minimum required for study entry.

Table 4-4: Around-the-Clock and Oral Rescue Medication at Study Entry in Patients With Noncancer-Related Breakthrough Pain

	ATC medication type		
ATC or rescue opioid medication	**Oral opioids**	**Transdermal fentanyl**	**Intrathecal medications**
ATC medication dose, mg/day[a]	n=688	n=223	n=30
Mean (SD)	211.1 (209)	209.3 (139)	—
Median	120	180	—
Min, max	15[b], 2160	60, 1440	—
Oral rescue medication dose, mg/episode[a]	n=683	n=220	n=29
Mean (SD)	27.0 (27.3)	31.8 (102)	35.2 (47.6)

[a] Oral morphine equivalent.
[b] There were 7 patients whose ATC total daily dose was less than 60 mg/day in oral morphine equivalents; 3 patients had protocol violations, 2 patients had the hourly dose amount recorded instead of the total daily dose, and 2 patients were considered to meet the criteria for opioid tolerance on the basis of acceptable differences in conversion factors.
ATC=around-the-clock; SD=standard deviation, min=minimum; max=maximum.

The most frequently used ATC opioid medications at study entry were oxycodone (31%), fentanyl (24%), morphine (22%), and methadone (15%). More than approximately 10% of patients were taking more than 1 ATC opioid medication. The most frequently used opioids for BTP were oxycodone (40%), hydrocodone (34%), or fentanyl (11%) (Table 4-5).

Table 4-5: Breakthrough Pain Medication at Study Entry in Patients With Noncancer-Related Breakthrough Pain

ATC opioid	**Number (%) of patients (N=941)**
Oxycodone	380 (40)
Hydrocodone	321 (34)
Fentanyl (ACTIQ)	105 (11)
Morphine	70 (7)
Hydromorphone	54 (6)
Tramadol	31 (3)
Propoxyphene	30 (3)
Codeine	15 (2)
Methadone	11 (1)
Meperidine	5 (<1)
Butorphanol	1 (<1)
Meperidine/Promethazine	1 (<1)
Pentazocine	1 (<1)

4.3 Efficacy Results From Studies of Noncancer-Related Breakthrough Pain

4.3.1 Overall Summary of Efficacy in Noncancer-Related Breakthrough Pain

Efficacy data were analyzed for 237 opioid-tolerant patients with noncancer-related BTP.

All 3 efficacy studies demonstrated consistent results with statistically significant and clinically relevant improvements in pain intensity and pain relief in favor of FENTORA. The results from the pivotal study are as follows:

- primary variable $SPID_{60}$ statistically significant ($p<0.0001$) in favor of FENTORA
- pain intensity difference statistically significant ($p=0.0132$) after 15 minutes in favor of FENTORA, with treatment effect increased through 1 hour and maintained through 2 hours
- the proportion of episodes with clinically relevant reduction in pain intensity statistically significant ($p<0.05$) in favor of FENTORA, achieved as early as 5 minutes and maintained thereafter
- mean pain relief scores over time statistically significant ($p<0.05$) in favor of FENTORA as early as 5 minutes after administration
- meaningful pain relief statistically significant ($p<0.05$) in favor of FENTORA as early as 10 minutes after administration

4.3.2 Pain Intensity Assessments

4.3.2.1 Summed Pain Intensity Difference Over Time (Primary Efficacy Variable)

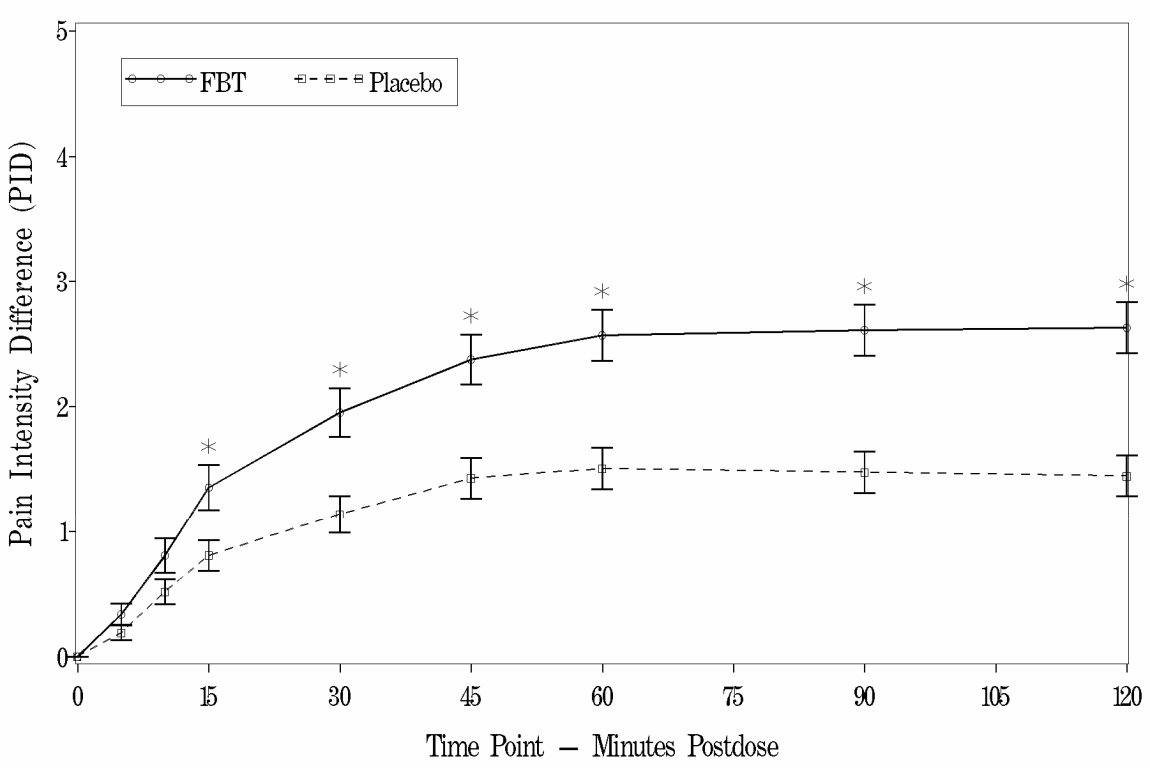
Pain intensity was recorded by patients in their diaries on a scale from 0 (no pain) to 10 (the worse pain imaginable). Baseline was the value recorded immediately prior to administration of study drug. Average pain intensity just prior to administration of study drug during the double-blind treatment periods was similar for all double-blind treatment periods across studies (overall range 6.9 to 7.1).

In pivotal study 3052, the primary analysis of the $SPID_{60}$ after 12 weeks of treatment showed a statistically significant ($p<0.0001$) difference between FENTORA and placebo treatment in favor of FENTORA. The results were similar after 4 and 8 weeks of treatment in study 3052 and for studies 3041 and 3042. Treatment with FENTORA was effective in all subgroups.

4.3.2.2 Pain Intensity Difference

In pivotal study 3052, after 12 weeks of treatment there was a statistically significant difference ($p=0.0132$) as early as 15 minutes in favor of treatment with FENTORA. The treatment effect increased through 1 hour and was maintained through 2 hours (Figure 4-3).

Figure 4-3: Mean (SEM) Pain Intensity Difference at Each Time Point by Treatment After 12 Weeks of Treatment in Study 3052

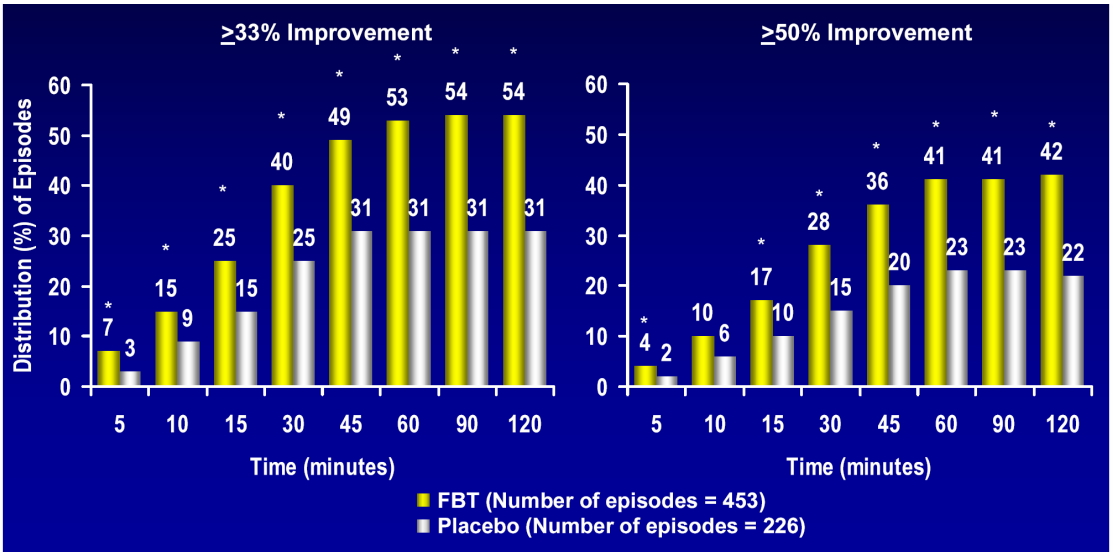


N=79; SEM=standard error of the mean.
FENTORA is also referred to as FBT (fentanyl buccal tablet).
NOTE: Asterisks (*) indicate time points where the difference between FENTORA and placebo is statistically significant ($p<0.05$).

In pivotal study 3052, effects of treatment with FENTORA as assessed by pain intensity difference were seen within the first 30 minutes for all double-blind treatment periods (4, 8, and 12 weeks), and as early as 10 minutes in supportive studies 3041 and 3042.

Clinically meaningful response was defined as at least 33% reduction in pain intensity from baseline. In study 3052, after 12 weeks of treatment, a greater proportion of episodes treated with FENTORA achieved this level of reduction in pain intensity as early as 5 minutes (Figure 4-4). In addition, similar results were achieved when applying the more stringent criterion of 50% reduction in pain intensity.

Figure 4-4: Moderate (33% or More) and Substantial (50% or More) Improvement at Each Time Point by Episode After 12 Weeks of Treatment in Study 3052

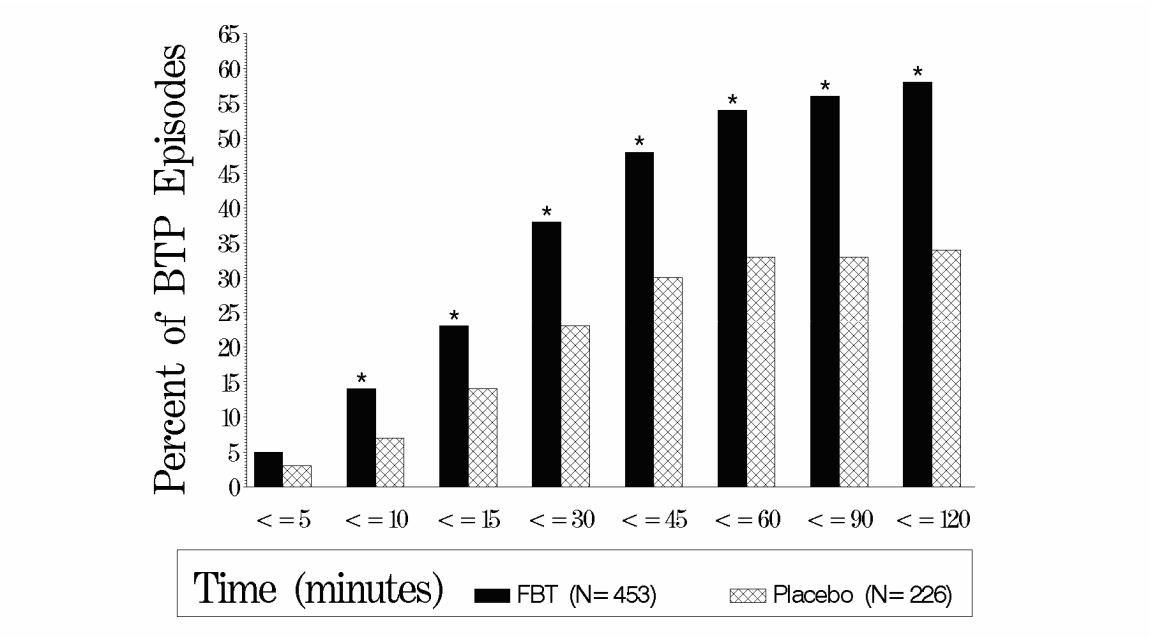


FENTORA is also referred to as FBT (fentanyl buccal tablet).
NOTE: Asterisks (*) indicate time points where the difference between FENTORA and placebo is statistically significant ($p<0.05$).

4.3.3 Meaningful Pain Relief

After 12 weeks of treatment in study 3052, meaningful pain relief as defined by each patient for episodes treated with FENTORA was consistently reported earlier than for episodes treated with placebo (Figure 4-5). In addition, results for meaningful pain relief were consistently seen across double-blind treatment periods in all studies, with 54% to 69% of episodes treated with FENTORA having pain relief reported as meaningful by 120 minutes posttreatment.

Figure 4-5: Cumulative Percentage of Episodes in Which Patients Reported Meaningful Pain Relief After 12 Weeks of Treatment in Study 3052



FENTORA is also referred to as FBT (fentanyl buccal tablet).
NOTE: The asterisk indicates each time point where the difference between the FENTORA and placebo is statistically significant (p-value <0.05).

4.3.4 Achievement of a Successful Dose

In the clinical studies, FENTORA was individually titrated for each patient to a dose that was effective and tolerable. Eighty-three percent of patients were able to achieve a successful dose, which was 600 or 800 mcg for the majority (56%) of patients.

Among the 176 patients (19% of 941 patients treated with FENTORA) who withdrew during the titration period, 50 (5% of the 941 patients) patients withdrew because they were unable to identify an effective dose.

While patients taking higher doses of ATC opioid medication at baseline generally required higher doses of FENTORA, no simple linear relationship could be determined and there is considerable variability. This observation indicates that selection of an opioid dose for BTP on the basis of the dose of the patient's current ATC opioid medication, which is conventional practice, is not appropriate for FENTORA.

The distribution of FENTORA doses found to be successful were similar among the different primary pain diagnoses.

4.3.5 Dose Characteristics of FENTORA Over Time

Among the 941 treated patients, 766 took at least 1 dose of study drug in either a double-blind or an open-label period. All 4 studies contributed data up to 3 months; data beyond 3 months were from study 3040 only.

In the clinical studies, 33% of patients had their dose of FENTORA increased at least once. The mean daily dose of FENTORA increased from 2162 mcg/day during the first 3 months of treatment, to 2885 mcg after 9-12 months of treatment, and to 3088 mcg/day after 15-18 months of treatment. Consistent with the known effects of chronic opioid use, increases in ATC medication dose paralleled adjustments in the FENTORA daily dose.

It is not known to what degree tolerance to analgesic effects of opioids contributed to the increase in dose of either ATC medication or FENTORA. Of note, across studies, only 19 (2%) patients withdrew during the posttitration periods due to lack of efficacy over a period of up to 18 months.

4.3.6 Clinical Relevance of the Results of Outcome Measures

The results from the Phase 3 studies indicate that the analgesic profile of FENTORA is appropriate for the effective management of a typical episode of BTP, as evidenced by onset of analgesic activity, consistency of response across measures, consistency of response over the observation period, and the clinical relevancy of the responses. Patients participating in the clinical studies overwhelmingly (>70%) across studies indicated a preference for FENTORA over the BTP medication they were taking prior to study entry. The results from these studies in patients with noncancer-related BTP are consistent with those seen previously in Cephalon-sponsored studies in patients with cancer-related BTP, both in regard to onset of activity and duration of effect (Portenoy et al 2006, Slatkin et al 2007).

These observed responses show that FENTORA provides both an appropriate onset of analgesia for BTP and a continued beneficial effect to patients with chronic noncancer-related pain and BTP.

4.4 Safety Data From Clinical Studies of Noncancer-Related Breakthrough Pain

4.4.1 Overall Summary of Safety in Noncancer-Related Breakthrough Pain

Overall, safety data from the Phase 3 studies indicate the following:

- Nausea, vomiting, constipation, dizziness, and somnolence were common adverse events seen with FENTORA treatment.
- With FENTORA's buccal route of administration, application site reactions were commonly seen; however, the majority of events were mild to moderate, did not lead to discontinuation of study drug, and did not appear to have long-term consequences.

- Six patients died during the clinical studies, with no deaths attributed to treatment with FENTORA.
- Fourteen percent of patients had serious adverse events that were mostly attributable to the patients' comorbidities.
- Drug withdrawal syndrome was reported by 20 (3%) patients, treatment related for 11 and severe for 9.
- Ten patients had serious adverse events associated with opioid overdose and all of these patients recovered with no residual effect. The partner of a study participant experienced a fatal overdose after diverting FENTORA from a clinical study patient.
- Of the 147 (16%) of patients who withdrew from a study due to adverse events, for 109, the events were treatment related, and for 30, the events were serious.
- The pattern of adverse events observed with FENTORA treatment did not appear to differ appreciably over time.
- Treatment with FENTORA appeared to have no untoward effect on clinical laboratory test results or vital signs measurements.

4.4.2 Extent of Exposure

In the 4 FENTORA Phase 3 clinical studies, 941 patients received 1 or more doses of FENTORA, with half of the patients treated for at least 6 months (Table 4-6). In conjunction with the safety data from the studies in cancer-related BTP, these exposure data meet the requirements set forth by the FDA.

Table 4-6: FENTORA Exposure Data

No. of patients treated	**941**
Mean duration of treatment (including titration), months (days)	8 (241.3)
Total exposure, patient-treatment years	621.62
≥1 month, n (%)	728 (77)
≥6 months, n (%)	472 (50)
≥12 months, n (%)	319 (34)
≥15 months, n (%)	214 (23)

During titration, 91% of the 941 enrolled patients received a maximum FENTORA dose of 400 mcg or higher, with 63% of patients receiving a maximum dose of 800 mcg. The mean duration of the titration period was similar among the FENTORA doses (range 5.8 to 7.4 days). A total of 766 patients entered a posttitration period.

4.4.3 Adverse Event Profile

4.4.3.1 Most Common Adverse Events

The most frequently occurring adverse events observed in the FENTORA are those commonly associated with fentanyl and other opioids (Table 4-7).

Table 4-7: Adverse Events That Occurred in at Least 5% of Patients With Chronic Noncancer-Related pain and Breakthrough Pain

System organ class Adverse event preferred term	Number (%) of patients (N=941)
Number (%) of patients with at least 1 adverse event	**802 (85)**
Gastrointestinal disorders	
Nausea	222 (24)
Vomiting	114 (12)
Constipation	67 (7)
Diarrhoea	52 (6)
General disorders and administration site conditions	
Application and instillation site reactions[a]	116 (12)
Oedema peripheral	57 (6)
Fatigue	46 (5)
Infections and infestations	
Urinary tract infection	60 (6)
Nasopharyngitis	53 (6)
Upper respiratory tract infections	52 (6)
Sinusitis	47 (5)
Bronchitis	45 (5)
Musculoskeletal and connective tissue disorders	
Back pain	105 (11)
Arthralgia	66 (7)
Pain in extremity	61 (6)
Nervous system disorders	
Dizziness	107 (11)
Headaches	100 (11)
Somnolence	95 (10)
Psychiatric disorders	
Depression	49 (5)
Insomnia	48 (5)

[a] Includes application site irritation (4%); pain (3%); ulcer and erythema (2% each); and reaction, vesicles, anaesthesia, discoloration, bleeding, discomfort, swelling, nodule, and paraesthesia (<1% each).
NOTE: Patients are counted only once in each preferred term category.

Adverse events commonly associated with opioid use include constipation, dizziness, nausea, somnolence, and vomiting. Nausea was the most frequently occurring (24%) adverse event in this category. The median number of events per patient for all of the aforementioned opioid-related events was 1.0. No patient had more than 6 episodes of any of the adverse events. The median time to onset of the first episode occurred within the first 7 days of treatment for all of the events except constipation (102 days) and vomiting (53.5 days). The median duration of the events was 2.0 days or less, except for constipation, which had a median duration of 10.5 days.

With the exception of application site disorders (see section 4.4.3.2(e)), the overall adverse event data observed in these studies are consistent with the known safety profile of fentanyl. The overall adverse event profile is also impacted by background opioid treatment, co-existing medical conditions, and concomitant medications. The pattern of adverse events observed is also consistent with that observed in studies of patients with cancer-related BTP.

Evaluation of adverse events in special groups and situations was performed on the primary patient population of opioid-tolerant patients with chronic noncancer-related pain and BTP. Parameters considered included age, sex, race, BMI, primary pain diagnosis, and average daily FENTORA dose. These analyses showed that there is no difference in the adverse event profile of FENTORA in these population subgroups.

4.4.3.2 Adverse Events of Special Interest

Adverse events of special interest (ie, deaths, other serious adverse events, overdose, adverse events of drug withdrawal syndrome, and adverse events associated with the application site) are discussed below.

(a) Deaths

Six patients died during clinical studies (Table 4-8). All 6 patients had participated in long-term open-label study 3040. Five deaths were cardiac related and 1 death was attributed to infection (ie, pneumonia). None was considered related to FENTORA treatment by the respective study investigators. A seventh patient, patient 024005 (study 3040) committed suicide prior to receiving study drug. Specific information on his death is not provided here. In addition, Cephalon was notified of a death resulting from study drug overdose in the husband of a patient participating in study 3040 one year after the patient began the study; the husband had a history of drug abuse.

Table 4-8: Listing of Deaths of Patients With Noncancer-Related Pain and Breakthrough Pain

Patient number	Age (y)/Sex	Exposure to study drug (days)	Adverse event(s) leading to death	Relationship to study drug
Study 3040				
021006	52/M	556	Myocardial infarction	Not related
021008	45/F	62	Cardiac arrest	Not related
040006	56/M	132	Pneumonia staphylococcal	Unlikely
043010	57/M	12	Myocardial infarction	Unlikely
409004	51/M	361	Cardiac arrest, coma	Not related
504005	67/F	28	Acute myocardial infarction	Unlikely

F=female; M=male; y=year.
NOTE: No deaths occurred in study 3052, 3041, or 3042.

Brief narratives of the 6 deaths follow:

- Patient 021006 (study 3040), a 52-year-old white man, had chronic back pain at study entry. Concomitant conditions included Parkinson's disease, arteriosclerotic

cardiovascular disease, and hypertension. Other relevant medical history included transient ischemic attack, carotid endarterectomy, coronary stent, aortic bypass, peripheral vascular disease, dyslipidemia, cholecystectomy, bladder infection, depression, and type II diabetes (controlled by diet). The patient achieved a successful FENTORA dose of 600 mcg. On day 96, the patient experienced mild blood cholesterol increased (nonserious) and was diagnosed with severe arteriosclerosis. He had a coronary artery bypass graft on day 465. On day 545, the patient had a severe myocardial infarction, which was fatal. The investigator considered this event not related to study drug.

- Patient 021008 (study 3040), a 45-year-old white woman, had chronic pain attributed to dermatomyositis. Other relevant medical history included fibromyalgia, hypertension, transient ischemic attack, arteriosclerotic cardiovascular disease, grand mal seizure, and depression. On day 62, the patient underwent a Whipple procedure for removal of a severe, benign pancreatic cyst. Study drug was discontinued and the patient was discharged from the hospital on day 82. Two days later (day 84), she was readmitted to the hospital due to dehydration, weakness, and an inability to tolerate food. The patient was discharged on day 87. On day 90, she had a severe cardiac arrest and died in her sleep. The cardiac arrest occurred 28 days after her last dose of study drug.

- Patient 040006 (study 3040), a 56-year-old American Indian man, had chronic pain due to osteoarthritis. His relevant medical history included asthma, thyroid cancer with metastases to the lung, shortness of breath, and diabetes mellitus. On day 128, the patient developed moderate upper respiratory tract congestion. The upper respiratory tract congestion worsened and on day 132, the patient developed severe staphylococcal pneumonia and was hospitalized. That same day, he arrested and could not be resuscitated.

- Patient 043010 (study 3040), a 57-year-old black man, had chronic pain attributed to complex regional pain syndrome (predominantly neuropathic). Relevant medical history included hypercholesterolemia and hypertension. His cholesterol value at screening was 219 mg/dL (reference range: 130 mg/dL-200 mg/dL). He achieved a successful FENTORA dose of 800 mcg on day 8, and entered the maintenance treatment period on day 9. At the day-9 visit, the patient's blood pressure was 136/74 mm Hg and pulse rate was 72 beats per minute (bpm). On day 12, the patient died. The suspected cause of death was a myocardial infarction based upon the patient's history of hypertension and hyperlipidemia as well as his family history.

- Patient 409004 (study 3040), a 51-year-old white man, had diabetic peripheral neuropathy. His relevant medical history included coronary artery bypass graft-3 vessel, hypercholesterolemia, right carotid endartectomy, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, type I diabetes, and depression. The patient's last dose of study drug was taken on day 340. On day 341, the patient had a serious adverse event of severe cardiac arrest and coma that were fatal; he died on day 342.

- Patient 504005 (study 3040), a 67-year-old white woman, had chronic low back pain. Her relevant medical history included myocardial infarction, ejection fraction of 30%, pacemaker/automatic implantable cardiac defibrillator, cerebral vascular accident, hypertension, coronary artery disease, current smoker, chronic obstructive pulmonary disease, congestive heart failure, fibromyalgia, type II diabetes, elevated cholesterol, hyperlipidemia, and depression. She completed double-blind study 3042 at a successful FENTORA dose of 800 mcg and entered open-label study 3040. On day 12 of study 3040, the patient was found dead on the couch in her apartment, where, according to the coroner, it appeared that she had been dead for several hours to days. Given the patient's history, acute myocardial infarction was given as the cause of death. The serious adverse event leading to death was recorded as a severe acute myocardial infarction.

In addition, the husband of patient 024031 (study 3040) was found dead on 4 April 2006. He was a 54-year-old man with a history of drug abuse. The patient informed the investigator that she believed her husband took her study drug (800-mcg tablets), as 12 to 18 tablets were missing. The autopsy report confirmed that this individual died from fentanyl overdose (plasma fentanyl concentration of 10 ng/mL). The patient was withdrawn from the study due to this event.

(b) Other Serious Adverse Events

A total of 129 (14%) patients with chronic noncancer-related pain and BTP experienced 1 or more serious adverse events (Table 4-9). This includes 6 patients who had serious adverse events with fatal outcomes (see section 4.4.3.2(a) above). Serious adverse events reported in 4 or more patients included myocardial infarction, vomiting, nausea, chest pain, drug withdrawal syndrome, cholelithiasis, pneumonia, cellulitis, gastroenteritis, back pain, and syncope. However, only pneumonia (n=7) was reported as serious in more than 5 patients. Most of these serious adverse events were considered attributable to the patients' comorbidities. Twenty patients reported drug withdrawal syndrome; the event was considered serious in 4 (20%) of them. These results suggest that although symptoms of opioid withdrawal occurred in these opioid-tolerant patients, they were typically not serious. (See section 4.4.3.2(d) below for further discussion of opioid withdrawal.)

Table 4-9: Serious Adverse Events That Occurred in at Least 2 Patients

System organ class Adverse event preferred term	Number (%) of patients (N=941)
Number of patients with at least 1 serious adverse event	**129 (14)**
Cardiac disorders	
Myocardial infarction	4 (<1)
Atrial fibrillation	3 (<1)
Angina pectoris	2 (<1)
Cardiac arrest	2 (<1)
Gastrointestinal disorders	
Vomiting	5 (<1)
Nausea	4 (<1)
Abdominal pain	3 (<1)
Abdominal pain lower	3 (<1)
Diarrhoea	2 (<1)
Ileus	2 (<1)
Intestinal obstruction	2 (<1)
General Disorders and Administration Site Conditions	
Chest pain	5 (<1)
Drug withdrawal syndrome	4 (<1)
Hepatobiliary disorders	
Cholelithiasis	5 (<1)
Biliary dyskinesia	2 (<1)
Infections and Infestations	
Pneumonia	7 (<1)
Cellulitis	4 (<1)
Gastroenteritis	4 (<1)
Pyelonephritis	3 (<1)
Sepsis	3 (<1)
Kidney infection	2 (<1)
Injury, Poisoning and Procedural Complications	
Accidental overdose	3 (<1)
Post procedural haemorrhage	2 (<1)
Radius fracture	2 (<1)
Metabolism and Nutrition disorders	
Dehydration	3 (<1)
Musculoskeletal and Connective Tissue disorders	
Back pain	4 (<1)
Arthralgia	2 (<1)
Neck pain	2 (<1)
Nervous System disorders	
Syncope	4 (<1)
Migraine	3 (<1)
Coma	2 (<1)
Transient ischaemic attack	2 (<1)
Unresponsive to pain stimuli	2 (<1)

Footnotes are presented at the end of the table. (continued)

Table 4-9: Serious Adverse Events That Occurred in at Least 2 Patients (Continued)

System organ class Adverse event preferred term	Number (%) of patients (N=941)
Psychiatric disorders	
Depression	3 (<1)
Bipolar disorder	2 (<1)
Drug dependence	2 (<1)
Mental status changes	2 (<1)
Suicidal ideation	2 (<1)
Suicide attempt	2 (<1)
Respiratory, Thoracic and Mediastinal disorders	
Dyspnoea	2 (<1)
Respiratory failure	2 (<1)
Vascular disorders	
Hypotension	2 (<1)

NOTES: Preferred terms are sorted by descending order of incidence within system-organ class. Patients are counted only once in each preferred term category and only once in each system organ class.

(c) Overdose

Ten patients had serious adverse events associated with opioid overdose while participating in a clinical study of FENTORA (Table 4-10). All of these patients recovered with no residual effect. Brief descriptions of the adverse events of overdose are provided in the appendix (section 9.1).

Table 4-10: Listing of Patients Who Had Serious Adverse Events Associated With Opioid Overdose

Patient number	Age (y)/Sex	Onset day	Relationship to study drug[a]
Study 3040			
003021	47/F	11	Possibly related
019004	47/M	341, 345	Not related
019010	67/F	490	Not related
025003	54/F	131	Not related
026010	63/F	107	Possibly related
030008	45/F	601	Not related
511003	54/F	285	Probably related
513017	54/M	52	Probably related
Study 3042			
503003	60/M	6	Possibly related
Study 3052			
026008	53/F	99	Definitely related

F=female; M=male; y=year.
[a] Investigator assessment.
NOTE: In addition, Cephalon was notified of a death resulting from study drug overdose in the husband of a patient participating in study 3040 one year after the patient began the study; the husband had a history of drug abuse.

The factors contributing to overdose included suicide attempt, polysubstance abuse, and having multiple dose strengths of FENTORA available to the patient at one time. For some of the cases, it is not possible to know the exact circumstances of the event.

(d) Drug Withdrawal Syndrome

Withdrawal symptoms are a known consequence of abrupt cessation of opioids after regular usage. Adverse events often associated with opioid withdrawal include anxiety, yawning, perspiring, rhinorrhea, restlessness, piloerection, stomach cramps, hot or cold flashes, and tremor. For patients who experienced any symptoms of opioid withdrawal, the study investigators were instructed to report these adverse events as drug withdrawal syndrome rather than to report each symptom (as specified above) by its individual preferred term.

Twenty (3%) patients were reported to have drug withdrawal syndrome posttitration. For 11 of the patients, the investigator considered the event related to study drug treatment; for 9 of the patients who had drug withdrawal syndrome, the event was severe. For 5 patients, drug withdrawal syndrome was considered to be both related and severe.

In many cases, the study investigator indicated that the drug withdrawal syndrome was associated with cessation of ATC medication, or that the exact medication leading to withdrawal could not be determined.

(e) Application Site Adverse Events

Of the 941 opioid-tolerant patients with chronic noncancer-related pain and BTP, 116 (12%) had application site adverse events (Table 4-11). The most frequently reported application site events were irritation (4%), pain (3%), ulcer (2%), and erythema (2%).

Table 4-11: Application Site Adverse Events

Adverse event preferred term	Number (%) of patients (N=941)
Number of patients with application site adverse events	**116 (12)**
Application site irritation	37 (4)
Application site pain	31 (3)
Application site ulcer	22 (2)
Application site erythema	16 (2)
Application site reaction	7 (<1)
Application site vesicles	7 (<1)
Application site anaesthesia	4 (<1)
Application site discolouration	3 (<1)
Application site bleeding	2 (<1)
Application site discomfort	2 (<1)
Application site swelling	2 (<1)
Application site nodule	1 (<1)
Application site paraesthesia	1 (<1)

NOTES: Analysis includes data from studies 3052, 3041, 3042, and 3040. Patients are only counted once for each preferred term.

The majority (87%) of application site events resolved without sequelae and only 11 (1%) patients withdrew from a study because of the event.

These results indicate that for those patients who have application site reactions, the majority of events are mild to moderate, do not lead to discontinuation of study drug, and do not appear to have long-term consequences.

4.4.3.3 Adverse Events Leading to Withdrawal From the Study

A total of 147 (16%) patients with chronic noncancer-related pain and BTP withdrew from a study due to an adverse event. Adverse events leading to withdrawal from the study were considered to be treatment related in 109 patients and serious in 30 patients. Adverse events that led to study drug discontinuation in 1% or more of patients were nausea (4%), vomiting (3%), dizziness (1%), and headache (1%).

With the exception of application site adverse events, the type of adverse events for which patients withdrew was expected in a population with chronic pain and multiple comorbid conditions using ATC opioid therapy.

4.4.4 Long-Term Safety

During the posttitration period, the overall incidence of adverse events decreased over time (0 to ≤3 months: 69%; >15 to ≤18 months: 47%). This may be related to a decrease in patient reporting of adverse events or a selection bias for the patients remaining in the study being less prone to experience adverse events. Most adverse events occurred at an incidence of less than 1% and showed minimal or no pattern related to duration of study participation. No adverse events increased in incidence in any appreciable way over time.

4.4.5 Evaluation of Clinical Program Data Related to Abuse Liability

Adverse events of substance abuse (including the preferred terms drug dependence and polysubstance dependence) were reported for 4 patients participating in the FENTORA clinical studies. Since the frequency of actual adverse events of substance abuse was so low, retrospective post hoc review of the clinical study database was conducted in order to identify any potential events of substance abuse. In addition, review was performed to identify significant safety events associated with overdose, and behaviors that might signify potential loss of control.

A number of authors have proposed the identification of aberrant drug behaviors as a means of predicting (and preventing) the development of a substance abuse disorder (Chabel et al 1997, Ives et al 2006, Michna et al 2004, Passik et al 2002, Portenoy 1996, Webster and Webster 2005). The descriptions of aberrant behaviors in the medical literature, however, have been derived from observations made in the clinical practice setting.

In order to identify potential aberrant behaviors as they occurred in the clinical study setting and in order to identify all events possibly indicative of substance abuse or overdose, complete data listings from the FENTORA clinical studies were reviewed. The

methods for categorizing observations related to potential substance abuse in the database are provided below, with the categories for aberrant behaviors created on the basis of descriptions of aberrant behaviors in the medical literature.

Events possibly indicative of substance abuse or overdose	**Aberrant behaviors involving the use of study drug**	**Aberrant behaviors not involving the use of study drug**
Abuse/dependence (described by investigator)	Fear of addiction	Motor vehicle accident
	Report of study drug theft	Discharged from pain-management practice
Positive urine drug screen	Report of lost study drug	Using nonprescribed medication
Overdose	Overuse of study drug	Lost to follow-up
	Unapproved use of study drug for another symptom	Seeking prescriptions from other sources
	Unreliability	Acquiring opioids from other medical sources

Within the FENTORA clinical studies, a total of 30 (3%) patients were identified with events possibly indicative of substance abuse or overdose as follows: 13 (1%) patients had positive urine drug screens, 10 (1%) patients had drug overdose, and 8 (<1%) patients were reported by the investigator to have abuse/dependence including 1 (<1%) patient who also had a drug overdose. Because the incidence of these events was relatively low, the ability to identify associated risks factors associated was limited.

Aberrant behaviors not involving the use of study drug were identified as follows: overuse of study medication in 44 (5%) patients, medication theft in 35 (4%) patients, fear of addiction in 6 (<1%) patients, lost study drug in 5 (<1%) patients, unreliability in 2 (<1%) patients, and unapproved use of drug to treat another symptom in 2 (<1%) patients.

Aberrant behaviors not related to the use of study drug were identified as follows: 33 (4%) patients were lost to follow-up, 4 (<1%) patients had motor vehicle accidents, 4 (<1%) patients used nonprescribed medications, 2 (<1%) patients were discharged from their pain-management practice, 1 (<1%) patient sought prescriptions from other sources, and (<1%) patient acquired opioids from another medical source.

Data from all of the patients identified were pooled in order to allow for analysis of potential risk factors. Demographic and baseline characteristics of the patients identified revealed that younger patients (≤42 years old and >42 to ≤49 years old) were at increased risk (odds ratio 2.5 for ≤42 years old [95% CI 1.5-4.3] and 2.1 for >42 to ≤49 years old [95% CI 1.2-3.6]). In addition, the risk for events indicative of abuse or overdose and for displaying aberrant drug behavior did not increase over time in the FENTORA clinical studies. Review of abnormal medical history suggested that patients with a history of psychosis or mania were at higher risk (odds ratio 2.2 [95% CI 1.0-4.8]); patients who

had a history of anxiety or depression (which are prevalent conditions in this population) did not appear to be at higher risk for events indicative of abuse or overdose or for displaying aberrant behaviors.

In conclusion, the incidences of events possibly indicative of abuse or overdose and of potential aberrant drug behaviors observed in the FENTORA clinical studies are lower than the rates reported for patient with chronic pain receiving chronic opioid therapy in the clinical practice setting (Webster and Webster 2005). The increased risks associated with younger patients and with medical history of psychosis or mania are consistent with what has been previously described in the medical literature.

It is important to note that aberrant drug behaviors should not be considered surrogates for the diagnosis of abuse or addiction. Rather, identification of aberrant behaviors can provide information on patients who **may** be showing signs of loss of control.

4.4.6 Evaluation of Clinical Program Data Related to Diversion

4.4.6.1 Theft of Study Drug From Patients

Thefts of study drug were reported for 35 patients, and police reports were made for 22 of the occurrences. Five patients were withdrawn from the study at the discretion of the investigator or at the request of the sponsor due to the theft. Most thefts were reported to have been perpetrated by individuals 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 frequency of thefts outside the home indicates a need to provide patients with more specific instructions for safeguarding FENTORA in these situations.

4.4.6.2 Theft of Study Drug From Study Centers

Protocols for studies with FENTORA stipulated that the study drug be stored at the study centers in a securely locked, substantially constructed cabinet or enclosure appropriate for a Schedule II opioid. The investigator or designee was responsible for ensuring that deliveries of study drug and other study materials from the sponsor were correctly received and recorded, handled and stored safely and properly in accordance with the Code of Federal Regulations and local regulations. Despite these precautions, thefts of study drug occurred from 5 study centers, all of which were participating in study 3040.

This underscores that it is imperative that healthcare professionals be instructed to handle FENTORA appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

4.4.7 Clinical Safety Conclusions

Based on clinical study experience with FENTORA, the safety and tolerability profile observed in opioid-tolerant patients with noncancer-related BTP is consistent with the known profile of fentanyl in the population studied. Overall there were no unexpected findings with FENTORA.

5 POSTMARKETING DATA

Postmarketing data are received from many diverse sources, typically as individual case safety reports (ICSRs) that are reported voluntarily. The sources for these reports include spontaneous reports, the published medical and scientific literature, the internet, solicited reports such as patients assistance programs, drug compliance support or surveys, clinical study reports, epidemiology and observational studies, disease registries, regulatory databases, and licensor-licensee interactions. The events reported may be serious[2] (regulatory definition) or nonserious. Cephalon's postmarketing surveillance and pharmacovigilance activities for FENTORA include ongoing collection and evaluation of reported postmarketing adverse event reports with specific attention to the review and evaluation of serious adverse events, events related to overdose, abuse, or misuse, and actual or potential medication errors associated with the use of FENTORA. These specific data sources are targeted in order to be compliant with both standard regulatory reporting criteria and RiskMAP commitments and are evaluated in the context of available exposure data as a surrogate estimate of the treated population.

FENTORA received FDA approval on 25 September 2006 for use in opioid-tolerant patients with cancer-related BTP. The postmarketing data presented herein are for the reporting period from receipt of marketing authorization in the US through 31 December 2007. In addition, data submitted to FDA quarterly to meet RiskMAP commitments are also summarized.

5.1 FENTORA Postmarketing Exposure

The postmarketing usage of FENTORA in the US is estimated at approximately 2,175,482 patient-treatment days (Table 5-1). The total number of mcg sold was derived from the IMS National Prescription Audit (NPA) Plus database, which captures the projected volume of prescriptions dispensed from retail, mail service, and long-term care channels. This figure was derived from the total number of tablets of each mcg dosage strength sold to wholesalers during the reporting period (regardless of returns) to estimate patient-treatment days of exposure. The total number of mcg sold was divided by the average daily dose for the reporting period to calculate patient-treatment days.

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[2] A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the subject was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition

Table 5-1: Postmarketing Exposure Data

Reporting period	Total mcg sold	Average daily dose	Total patient-treatment days	Total patient-treatment years
Launch through 31 December 2007	4,067,786,400	1870 mcg	2,175,287	5960

Based on IMS NPA Plus data, 104,363 total prescriptions were dispensed for FENTORA for the period 1 October 2006 through 31 December 2007. Of those prescriptions, the 400-mcg strength was dispensed the most (27.34%), followed by 200 mcg (24.68%), 800 mcg (18.12%), 100 mcg (15.15%), and 600 mcg (14.69%) (Table 5-2). Twenty-one (0.02%) prescriptions were written for a 300-mcg dose.

Table 5-2: Number of Prescriptions Filled for FENTORA Since Product Launch

FENTORA dose[a]	Number of prescriptions through 31 December 2007	Percentage filled by strength
Total filled prescriptions	**104,363**	—
100 mcg	15,812	15.15%
200 mcg	25,754	24.68%
400 mcg	28,530	27.34%
600 mcg	15,336	14.69%
800 mcg	18,910	18.12%

[a] Twenty-one prescriptions were written for a 300-mcg dose.

5.2 Most Frequent Spontaneous Postmarketing Adverse Events

Cephalon's pharmacovigilance database was searched for all postmarketing reports received through 31 December 2007. Postmarketing adverse event reports include those received directly (ie, from consumers or healthcare professionals) or indirectly (ie, from licensing partners or regulatory authorities) as spontaneous reports or as case reports in the scientific literature. A total of 280 case reports for 535 adverse events were received during this reporting period. Of these 535 adverse events, 518 were nonserious.

The most frequently reported postmarketing adverse events during this reporting period were nausea, application site reactions in various forms, and other associated events occurring in the buccal cavity (Table 5-3).

Table 5-3: Most Frequently Occurring Postmarketing Adverse Events

Adverse event preferred term	Number of patients
Application site reactions	
Irritation	36
Ulcer	30
Vesicles	18
Pain	17
Bleeding	9
All other reactions	
Nausea	34
Drug ineffective	20
Drug ineffective for unapproved indication	19
Vomiting	17
Somnolence	13
Stomatitis	13
Drug prescribing error	11
Mouth ulceration	11
Dry mouth	10
Hyperhidrosis	10
Headache	9

SOURCE: Cephalon Pharmacovigilance Database (Clintrace 2.8).

With the exception of application site reactions, which are unique to this formulation of fentanyl citrate, the above reactions (ie, nausea, vomiting, somnolence, dry mouth, hyperhidrosis, and headache) are consistent with adverse reactions associated with opioid treatment. Overall, the type and frequency of postmarketing adverse events reported were similar to those seen in the clinical trial program.

In addition to the events listed above, 10 reports of drug withdrawal syndrome and 2 reports of drug dependence were received through 31 December 2007.

5.3 Postmarketing Serious Adverse Events

5.3.1 Overview of Postmarketing Serious Adverse Events

Ten postmarketing reports of events considered serious by regulatory criteria were received through 31 December 2007 (Table 5-4 [displayed in chronological order of receipt]). As of the datalock point, 6 of these events had fatal outcomes. As of March 2008, 1 additional report of an event with a fatal outcome was received after the datalock point and is included here for completeness (case US022230).

Table 5-4: Postmarketing Serious Adverse Event Reports

Case	Preferred term	Indication	Outcome
US019029	Chest discomfort Breast cancer metastatic	Cancer-related BTP	Fatal
US019172	Intentional overdose	None	Fatal
US019628	Constipation Drug ineffective Oral intake reduced Leiomyosarcoma metastatic Dysarthria Slurred speech Somnolence	Cancer-related BTP	Fatal
US019256	Serotonin syndrome	Chronic lower back pain	Recovered
US020030	Intentional overdose Loss of consciousness Drug dependence	NA	Recovered
US020247	Accidental overdose	Headache	Fatal
US020769	Cerebrovascular accident	NA	Not recovered
US021000	Overdose Loss of consciousness Respiratory arrest	Migraine	Recovered
US021127	Arrhythmia Multiorgan failure Anoxic encephalopathy	Chronic neck pain, migraines	Fatal
US021157	Drug toxicity	Chronic back pain and radiculopathy	Fatal
US022230[a]	Overdose resulting from drug diversion	NA	Fatal

SOURCE: Cephalon Pharmacovigilance database (Clintrace 2.8)
[a] Late-breaking report received after cut-off date is included for completeness.
BTP=breakthrough pain; NA=not applicable.

Three additional reports of serious events were received from a poison control center or as part of a postmarketing survey, which provided limited information for analysis. Two of the events reported (cases US021194, US021297) were deaths (Table 5-5).

Table 5-5: Reports Received as Poison Control Center Reports or Postmarketing Survey Reports

Case	Preferred term	Indication	Outcome
US021194	Drug abuse Somnolence Dyspnea	Unknown	Recovered
US021297	Death	Unknown	Fatal
US021440	Death	Unknown	Fatal

Brief case summaries are provided for the events reported where appropriate.

5.3.2 Serious Events With Fatal Outcomes

Of the 7 reported fatal events listed above (see Table 5-4), the following 2 were due to disease progression in patients with cancer taking FENTORA for BTP:

- Case US019029 describes a 32-year-old woman with a history of metastatic breast cancer with cerebral metastasis and anxiety who initiated 800 mcg of FENTORA daily. The patient was using a fentanyl patch concomitantly and experienced tightness and rigidity of the chest wall. Later, it was reported that the patient had since died due to disease progression from metastatic breast cancer.
- Case US019628 describes a 64-year-old man who initiated 400 mcg of FENTORA every 2 hours as needed up to 8 times daily for the treatment of breakthrough cancer pain (sarcoma). The patient reported lack of effect ("pain relief did not last long enough"), difficulty urinating, an inability to have a bowel movement, an inability to stay awake, and an inability to eat and drink. The patient took 2 tablets of FENTORA with 4 fentanyl patches (50 mcg/hr) and experienced slurred speech and was unable to stay awake. He underwent eventual insertion of a neurostimulator implant for pain control. Approximately 6 weeks later it was reported that the patient had died.

In these reports, FENTORA appears to have been prescribed and administered as indicated. These deaths are not unexpected given the underlying disease.

Three reports associated with fatal outcomes were received with regard to patients using FENTORA for other conditions, and 2 reports were of partners of study patients who diverted study drug and had drug overdoses:

- Case US019172 describes a man (approximate age 45 to 55 years) with a history of drug addiction who had taken FENTORA from his partner, who had been using it for breakthrough cancer pain. The subject of this report took an intentional overdose of twenty-five 200-mcg FENTORA tablets in an apparent suicide attempt and died. The reporting physician indicated that the deceased had solicited medication during the previous week but was refused. No other information was provided.
- Case US020247 describes a 34-year-old woman who was prescribed FENTORA (400 mcg) for severe headache. The patient had been treated previously with two 800-mcg ACTIQ doses as needed for severe headache. She was not receiving other ATC opioids and periodically required 175 mg of pethidine (meperidine) at an urgent care clinic for headache relief. The physician switched her from ACTIQ to 400 mcg of FENTORA, with instructions to repeat the dose if there was no pain relief after 30 minutes. The patient's husband thought that the instructions stated that FENTORA could be taken every 30 minutes. The first dose was taken in the evening and the patient awoke very groggy in the morning. Sometime later that morning, the patient was found dead. Six FENTORA tablets (total 2400 mcg) were missing and thought to have been taken by the patient. The coroner concluded that the patient died of an accidental overdose of fentanyl.
- Case US021127 describes a 44-year-old woman who was prescribed 1 box of FENTORA (dosage unknown) per month for chronic pain related to a cervical spine

injury sustained in a motor vehicle accident. The patient had previously been treated with ACTIQ for years (time unknown). Concomitant medications included bupropion, lidocaine, duloxetine, and escitalopram. The patient's family found her unresponsive and cyanotic and had her taken to a local emergency room. Laboratory examinations were consistent with acute hepatotoxicity, acute renal failure, and disseminated intravascular coagulopathy. The patient died after 3 days of hospitalization in the intensive care unit. An autopsy revealed damage to the brain, liver, and small bowel attributable to lack of blood flow, and patchy fibrosis and hypertrophy within the heart muscle. The final cause of death was determined to be anoxic brain injury and multiorgan failure due to probable cardiac arrhythmia.

- Case US021157 describes a 40-year-old woman who was prescribed FENTORA 400 mcg every 8 hours for the treatment of BTP related to chronic back pain secondary to radiculopathy. This patient was a recent participant in a clinical study for a spinal stimulator; it had been removed and the patient was to undergo permanent placement of a spinal stimulator. Prior to initiating FENTORA therapy, the patient had been receiving pain therapy with fentanyl transdermal patch, 50 mcg/hour, 1-2 patches every 72 hours, for 1 year. During an office visit on [redacted], the physician wrote another prescription for FENTORA with instructions to the pharmacy not to fill it until [redacted] as the last prescription had been dispensed to the patient on [redacted]. The physician then learned through an obituary posted in the local newspaper that the patient had died on [redacted]. On autopsy, the cause of death was determined to be due to accidental acute fentanyl toxicity with coronary atherosclerotic disease as a contributory factor.
- Case US022230 describes a 44-year-old man with a history of alcohol and drug abuse and a previous suicide attempt who took his wife's medication and experienced an overdose. The subject of this report took 10 FENTORA tablets (strength unknown). He had been seen in an emergency room and referral to a "detox" facility was recommended; the patient refused and left against medical advice. The patient was subsequently found unresponsive in bed at home and was declared dead at the scene by emergency medical services. The cause of death was reported to be acute ethanol and opiate toxicity on autopsy.

Two of these reports (cases US019172, US022230) are of drug diversions within a household in which a patient had been prescribed FENTORA for BTP; 1 report (case US020247) is consistent with medication error; in 1 report (case US021127) the cause of death does not appear to be related to treatment with FENTORA; and 1 report (case US021157) is consistent with accidental overdose. People who had overdoses with FENTORA are further discussed below in section 5.4.

5.3.3 Other Serious Events

Three reports of serious events with an outcome of recovered and 1 with an outcome of not recovered were received during the reporting period (Table 5-6).

Table 5-6: Serious Events With an Outcome of Recovered or Not Recovered

Case Country Report Source	Age (y) Sex Race	Preferred terms[a]	Outcome	Case narrative
US019256 United States Medically confirmed	41 Male Unknown	Drug withdrawal syndrome[a] Serotonin syndrome	Recovered	41-year-old man who initiated FENTORA at 800 mcg daily for the treatment of chronic lower back pain and failed surgery. Concomitant medications included oxymorphone, zolpidem, gabapentin, amitriptyline, fentanyl, cyclobenzaprine, oxycodone, and sildenafil. The patient experienced delirium and presented to the emergency room, where naloxone was administered. The patient subsequently experienced a "violent withdrawal" and was treated with meperidine. It was concluded by a toxicologist at the hospital following unspecified results from a toxicology screen that the patient experienced serotonin syndrome. FENTORA was discontinued and the event resolved. The patient was later rechallenged with FENTORA without recurrence of the events.
US020030 United States Medically confirmed	34 Female Unknown	Intentional overdose[a] Loss of consciousness[a] Drug dependence[a]	Recovered	34-year-old woman who initiated FENTORA therapy, 800 mcg 3 to 6 times daily, for an unspecified indication. The patient overdosed by taking ⅓ of a box of 800 mcg of FENTORA (approximately 10 tablets or 8000 mcg) all at once. She subsequently passed out and was taken to the emergency room. The patient recovered and is currently seeking treatment for abuse.
US021000 United States Medically confirmed	34 Female White	Overdose[a] Loss of consciousness[a] Respiratory arrest[a]	Recovered	34-year-old woman with a medical history of severe neck injury resulting in trigeminal neuralgia, severe migraine headaches, and an occipital implantable nerve stimulator for pain control. Concomitant medications included oxycodone, hydrocodone, zolpidem, clonazepam and fentanyl transdermal patch. The patient had taken 1 dose of FENTORA (600 mcg) while driving; just before reaching the driveway to her home, she experienced a respiratory arrest. She was treated by emergency medical services with naloxone, taken to the emergency room, and discharged later that day. It was subsequently determined that the patient had not taken any other opioids on that day and had discontinued use of the fentanyl patch.
US020769 United States Medically confirmed	58 Female Unknown	Cerebrovascular accident[a]	Not recovered	58-year-old woman with a history of a stroke who initiated FENTORA 400 mcg. The patient was subsequently hospitalized due to a stroke and remained in a rehabilitation facility at the time of the report. Concomitant medications were not reported. Neither the underlying cause nor the severity of the stroke was known.

[a] Indicates primary preferred term.
y=years.

Respiratory depression occurred in cases US020030 and US021000 and delirium in case US019256. In case US020030, the respiratory depression occurred subsequent to the patient overdosing; in the other (case US21000), the patient was not opioid tolerant. Although the report of delirium was attributed to serotonin syndrome, many of the associated clinical features of this diagnosis are not reported (ie, autonomic manifestations, neuromuscular hyperactivity) and this diagnosis may have been an early "working diagnosis." The patient was later rechallenged with FENTORA and continued treatment with a selective serotonin reuptake inhibitor without recurrence of the reported events.

In case US020769, insufficient information is present for full evaluation. However, opioid use is not known to increase the risk for cardiovascular events. Pertinent details about medical history and risk factors for cardiovascular disease were not provided.

5.4 Reports of Overdose

Through 31 December 2007, Cephalon received 6 reports of overdose (Table 5-7). As ofMarch 2008, 1 additional report received after the datalock point is included for completeness. Four reports were received of events with fatal outcomes and in 3 reports, the outcomes were reported as recovered. All of the events reported are serious and are discussed above in sections 5.3.2 and 5.3.3.

Table 5-7: Postmarketing Reports of FENTORA Misuse or Abuse Resulting in Overdose

Case	ADR type	Condition	Dose	Outcome
US019172	Intentional overdose	None	5000 mcg	Fatal [a]
US020030	Intentional overdose	None	800 mcg	Recovered
US020247	Accidental overdose	Severe headache	400 mcg	Fatal [a]
US021000	Overdose	Severe pain from migraine and trigeminal neuralgia	600 mcg prn	Recovered
US021157	Accidental acute fentanyl toxicity	Chronic back pain second to radiculopathy	400 mcg	Fatal [a]
US021194	Overdose	Drug abuse	Unknown	Recovered
US022230[b]	Overdose resulting from drug diversion	None	Unknown	Fatal

[a] See section 5.3.2 for cases with fatal outcomes.
[b] Report received after the datalock point of 31 December 2007.
ADR=adverse drug reaction; prn=as needed (pro re nata).

5.5 Postmarketing Adverse Events Involving Medication Errors

5.5.1 Categorization of Medication Errors

Twenty-six reports of medication errors were received since the launch of FENTORA through 31 December 2007. Medication errors were classified according to the following preferred terms: drug dispensing error, drug prescribing error, incorrect route of administration, inappropriate schedule of drug administration, medication error, and accidental exposure. These events were categorized broadly as dispensing, prescribing, or use errors.

5.5.2 Drug Dispensing Errors

Three reports of drug dispensing errors (case US020247, US019609, US020449) were received through 31 December 2007. One report (case US020247) had a fatal outcome (see section 5.3.2); it is not clear whether the pharmacy label on the medication gave incorrect instructions for use or whether the medication was used improperly (use every 30 minutes vs repeat once in 30 minutes). The other 2 cases are reports of nonserious events in which the ACTIQ dose was converted to a FENTORA dose on a mcg-per-mcg basis in contrast to the conversion instructions in the US package insert (USPI).

5.5.3 Drug Prescribing Errors

Eleven reports of drug prescribing errors were received through 31 December 2007. In 5 reports, an inappropriate dose conversion from ACTIQ to FENTORA occurred; in 2 reports medication was prescribed to be taken by the sublingual route; in 1 report, the frequency of use was in error; and in 1 report, the instructions indicated that tablets may be split in half.

Subsequent to the launch of FENTORA, data are available demonstrating that the pharmacokinetic profile after administration of FENTORA via the buccal and sublingual routes are bioequivalent.

5.5.4 Drug Use Errors

Twelve reports of druguse error were received through 31 December 2007. This classification group includes the following preferred terms: incorrect route of administration, medication error, inappropriate schedule of drug administration, and accidental exposure. Ten of these reports were of incorrect route of administration. In 3 of these reports, the route was sublingual, and in 2 of these reports, the route was oral. Five of these reports were from poison control centers and the route was not specified. In the remaining 2 reports, 1 case of inappropriate schedule of drug administration (FENTORA was used hourly for BTP) and 1 case of accidental exposure (adult [see section 5.6]) were received.

5.6 Postmarketing Reports of Accidental Exposure

One report of accidental exposure to FENTORA was received as of 31 December 2007. In this report, medication was removed from its original packaging. The tablets were reportedly mistaken for aspirin by an elderly woman with Alzheimer's disease who experienced altered mental status, flushing, and sweating. However, upon evaluation of the patient in the emergency room, exposure to FENTORA was not confirmed and the reported spontaneous adverse events were attributed to lidocaine patches used concomitantly by this patient for treatment of unspecified chronic pain.

No reports of accidental pediatric exposure were received.

5.7 Postmarketing Reports of Drug Withdrawal Syndrome or Drug Dependence

5.7.1 Drug Withdrawal Syndrome

Ten reports of drug withdrawal syndrome were received through 31 December 2007. One report (case US019256) was a serious spontaneous adverse event describing a patient who experienced drug withdrawal and possible serotonin syndrome (see section 5.3.3). In all of these reports, the reported spontaneous adverse events are consistent with a diagnosis of drug withdrawal syndrome. In most of these cases, drug withdrawal symptoms were reported when a patient ran out of medication or was being switched from ACTIQ to FENTORA.

5.7.2 Drug Dependence

Two reports of drug dependence were received through 31 December 2007. Case US020030 was received in the context of a report of intentional overdose in a patient with a history of drug abuse (see section 5.3.3).

Case US021117 was received from a physician regarding an unknown number of patients (age and sex unknown) who took FENTORA therapy for the treatment of cancer-related BTP. The physician stated that she may have made her patients addicted to FENTORA at a higher dose than they likely needed. Although this case was reported as drug dependence, there is no evidence of persistent or sporadic intentional excessive use of the drug accompanied by harmful physical or psychological effects.

5.8 Surveillance Data

Both active and passive surveillance and monitoring systems are used for signal detection to track specific outcomes related to abuse and diversion. These systems augment Cephalon's routine pharmacovigilance activities and include reports from the American Association of Poison Control Centers (AAPCC; formerly Toxic Exposure Surveillance System [TESS]), Drug Abuse Warning Network (DAWN) Live!, and Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) system. Data received from the AAPCC are received by Cephalon's Global Pharmacovigilance & Epidemiology Department in the form of line listings and included in the database as ICSRs.

5.8.1 DAWN Live! Surveillance Data

The DAWN system is a public health surveillance system for monitoring drug-related emergency room visits for the nation and for selected metropolitan areas. The Office of Applied Studies (OAS) of the Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services, has been responsible for DAWN operations since 1992. DAWN Live! is a secure, internet-based query system used by participating hospital emergency rooms and medical examiners/coroners (ME/C) to track emergency room visits or deaths related to recent drug use. DAWN cases are found by retrospective review of all emergency room medical records or ME/C case files. These data are published by SAMHSA and are used by Cephalon to evaluate the nonmedical use of FENTORA.

DAWN Live! data for 2007 indicate that abuse or misuse is reported with low frequency in conjunction with FENTORA (Table 5-8).

Table 5-8: DAWN Live! Nonmedical Use Reports for Fentanyl Dose Forms and FENTORA

Medication	Reports in 2007
Opiates/opioids	**30328**
Opiates/opioids, unspecified	7113
Narcotic analgesics	
Buprenorphine/combinations	404
Codeine/combinations	751
Dihydrocodeine/combinations	1
Fentanyl	1013
Fentanyl	1013
ACTIQ	7
Fentanyl	217
Fentanyl lollipop	9
Fentanyl pops	1
Fentanyl suckers	3
FENTORA	2
Fentanyl NTA	774
All other analgesics	
Hydrocodone/combinations	5922
Hydromorphone/combinations	732
Meperidine/combinations	83
Methadone	6107
Morphine/combinations	1531
Opium/combinations	44
Oxycodone/combinations	6057
Pentazocine/combinations	7
Propoxyphene/combinations	522
All other narcotic analgesics/combinations NTA	41

[a] Because no fentanyl combination products are currently marketed, these values are the same.
DAWN=Drug Abuse Warning Network; NTA=not tabulated above.
NOTE: Nonmedical use of pharmaceuticals includes: taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose (overmedication), deliberate poisoning with a pharmaceutical by another person (malicious poisoning), taking a pharmaceutical prescribed for another individual (other), documented misuse or abuse of a prescription (other).

5.8.2 RADARS Surveillance Data

The RADARS system is a prescription drug abuse, misuse, and diversion surveillance system for collecting timely product-specific and geographically specific data. It is used to measure rates of abuse, misuse, and diversion throughout the US, contributing to the understanding of trends and aiding the development of effective interventions. Data are collected using the following 4 signal detection systems: Drug Diversion System, Key Informant Network System, Opioid Treatment Center System (methadone), and Poison

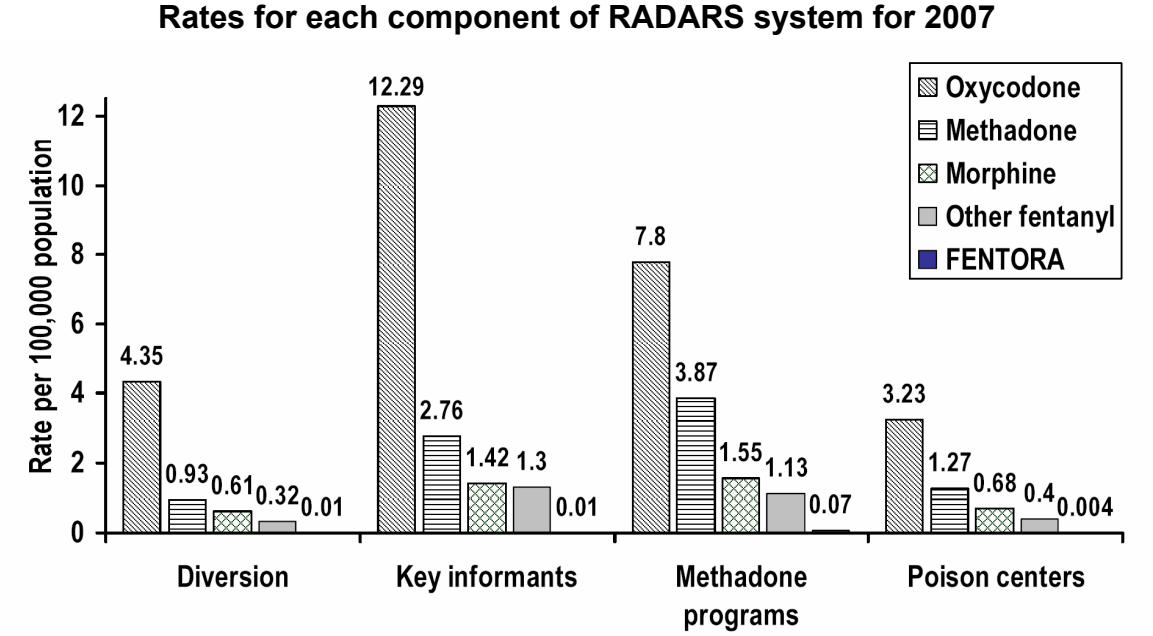
Center System. Cephalon uses these data to evaluate the effectiveness of the RiskMAP interventions and to develop new interventions if needed.

RADARS provides data for Cephalon to identify "signal sites" for FENTORA, other fentanyl products, and comparison drugs. A signal site is defined as any 3-digit ZIP code that meets or exceeds its signal threshold for any given drug in any given quarter. Rates are calculated by population (per 100,000 population) and by Unique Recipients of Dispensed Drugs (URDD) (per 1000 URDD). Signal thresholds are defined as follows:

- Drug Diversion and Key Informant Systems: 5 cases per 100,000 population
- Poison Center and Opioid Treatment Center Systems: 2 cases per 100,000 population

Population rates for 2007 for oxycodone, methadone, morphine, other fentanyl products, and FENTORA are shown below (Figure 5-1). These data include the previously summarized RMP data (ie, the data summarized in RMP quarterly reports 2, 3, and 4) and extend the analysis through 31 December 2007 (ie, data to be presented in RMP report 5).

Figure 5-1: Rates of Abuse From RADARS System (Per 100,000 Population) for 2007



RADARS=Researched Abuse, Diversion and Addiction-Related Surveillance.

No significant discrepancies between the data for population rates versus URDD rates were identified within each signal detection system. However, because URDD is calculated on the basis of projected data from national audit databases and other sources, a larger error results when the URDD is less than 25. A URDD of more than 25 must be observed in at least 3 consecutive quarters of 3-digit zip codes for the value to be meaningful. Only a few zip codes have been identified with a URDD of more than 25; therefore, the use of URDD to determine FENTORA signal sites is limited at this time.

Overall, RADARS data have not identified a signal for 3Q06, 4Q06, 1Q07, 2Q07, or 3Q07.

5.8.3 Conclusions About Surveillance Data

Data received from DAWN Live!, and the RADARS system indicate that abuse or misuse is reported with low frequency in conjunction with FENTORA. No signal sites have been identified for FENTORA.

5.9 Patient Populations Using FENTORA

5.9.1 Postmarketing Reports of Exposure to Opioid-Nontolerant Patients

Since the launch of FENTORA through 31 December 2007, Cephalon received 1496 initial evaluable spontaneous reports containing sufficient information to determine opioid tolerance. Using the USPI definition of opioid tolerance, approximately 86% (1288 of 1494) of reports involved patients who were opioid tolerant prior to starting FENTORA.

A total of 208 initial reports of FENTORA use in opioid-nontolerant patients were received. Most of these reports were received by Cephalon's Medical Services department and were for product questions or complaints. In the majority of cases (83%), no adverse events were reported in association with use of the drug. Of the initial 35 reports with an associated adverse event in opioid-nontolerant patients, most events were nonserious (91%). Fifteen initial reports were received for which it was confirmed that an ATC opioid was not concurrently used as part of a pain management plan. The conditions for treatment included migraine or headache, back pain, neck pain, neuropathy or noncancer neuropathic pain, abdominal pain, rheumatoid arthritis, and breast cancer. One report was received of a serious event in an opioid-naïve patient (case US020769 [see section 5.3 above]). However, 2 reports of serious events were received in opioid-experienced patients who may not have been taking ATC medications as prescribed (cases US020247, US021000) (see section 5.3.3 above).

Applying the USPI definition of "opioid tolerant" to the postmarketing environment presented some specific challenges. Among them, feedback from pain specialists indicated that criteria for deeming a patient opioid tolerant in clinical practice could vary widely among specialist practitioners. In some cases, patients who were opioid exposed and considered tolerant by the treating physician were receiving lower doses than that specified by the FENTORA prescribing information and Medication Guide. Despite the fact that the use of FENTORA by opioid-naïve patients is low, significant enhancements have been made to the current RiskMAP and the proposed RiskMAP to further minimize use in opioid-nontolerant patients.

5.9.2 Spontaneous Report Data and IMS National Prescription Audit Data on Patient Populations Using FENTORA

Spontaneous report data were used to evaluate the extent of use of FENTORA in the populations with the USPI indication and those with unlabeled conditions. These data

include inquiries from Cephalon's Medical Services department, and most of these reports (93%) are not associated with an adverse event. From launch through 31 December 2007, 1989 initial reports were received. In 225 reports (11.3%), the patients had a medical record indicating a diagnosis of cancer; in 281 reports (9%) the condition was unknown. Similarly, information obtained from IMS NPA data shows that 16% of patients with a corresponding medical record had a diagnosis of cancer listed in the past 12 months.

5.10 Current RiskMAP Quarterly Update Summaries

Upon approval of FENTORA for the management of BTP in opioid-tolerant patients with cancer, Cephalon committed to provide the FDA with quarterly reporting of the data to evaluate the tools implemented to determine the success in meeting the goals of the RiskMAP. Below are summaries of quarterly reports provided to the FDA, which include data observed and interventions implemented. All of the reports of deaths and medication errors have been described in the preceding sections.

FENTORA® Risk Minimization Action Plan, 1st Quarterly Report, 25 September 2006 – 31 December 2006

Observations

- Data obtained during the first 3 months of marketing of FENTORA was limited due to the initiation process for many of the tools.
- The initial postmarketing reports reflected that most prescribers were aware that patients are required to be opioid tolerant when FENTORA is prescribed; approximately 88% (275 of 314) of the reports received involved patients who were opioid tolerant prior to starting FENTORA. Data obtained from syndicated 3rd-party national audit data, specifically the IMS longitudinal prescription database (LRx) and the Electronic Medical Claims Switch database, indicated that 14.2% of prescriptions written for FENTORA were for patients with a medical history of cancer on the basis of International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD-9) diagnosis codes.
- No reports of accidental or inadvertent exposure, suspected misuse, or abuse were received. Additionally, there were no spontaneous or possibly-related study reports of death, accidental exposures, or serious adverse events associated with suspected abuse, misuse or diversion during the reporting period.
- Two spontaneous reports of suspected diversion (missing product) were received, including 1 report of 3 missing FENTORA cartons from a wholesale distribution facility and missing blister cards from a retail pharmacy.
- A single report of medication error was received in a female patient who had previously been treated with ACTIQ 1600 mcg and was switched from ACTIQ to FENTORA on a mcg-to-mcg basis (section 5.5.3). The report was promptly addressed by Cephalon, and a field representative called on the prescriber to educate him on FENTORA, the differences and conversion between ACTIQ and FENTORA, and the RiskMAP goals.

Interventions

- Multiple instances of inquiries to the call center, regarding the appropriate conversion from ACTIQ to FENTORA, were received by the Medical Services department. In response, additional education and retraining of field representatives was provided, reminding representatives to go over the Dosing and Administration section in the FENTORA package insert when calling upon prescribers.
- During the early part of the launch period, the Medical Services department received questions about administration of FENTORA. In response, an educational bulletin was issued to the field sales force and the Marketing department modified educational tools enhancing the information about the distinction in the bioavailability of FENTORA compared with that of ACTIQ.
- Reports of suspected diversion were promptly addressed by employing an investigation of the events in accordance with Cephalon's standard operating procedures (SOPs); there were no investigative findings suggestive of a loss within the Cephalon supply chain.

FENTORA® Risk Minimization Action Plan, 2nd Quarterly Report, 1 January 2007 – 31 March 2007

Observations

- Data obtained during the first 6 months of marketing of FENTORA were increased but still limited due to the initiation process for some of the tools (ie, surveys).
- Of the 308 reports received during the 2nd quarter reporting period with sufficient information to determine opioid tolerance, approximately 85% (262 of 308) involved patients who were considered opioid tolerant prior to starting FENTORA. Data obtained from syndicated 3rd-party national audit data, specifically the IMS LRx and the Electronic Medical Claims Switch database, indicated that 15.9% of prescriptions written for FENTORA were for patients with a medical history of cancer on the basis of ICD-9 diagnosis codes.
- No reports of accidental exposure or serious adverse events associated with misuse were identified. There was 1 report of a serious adverse event (drug withdrawal symptoms) in a 44-year-old female involving abuse of FENTORA in a Cephalon-sponsored clinical trial (section 4.4.6).
- Two spontaneous reports of suspected diversion were received, including 1 report of a 45- to 55-year-old male with a history of drug addiction who stole FENTORA tablets from his partner and apparently committed suicide and 1 report of the loss of product due to handling outside Cephalon's control (section 5.3.2).
- Two medication errors were reported and addressed. One report involved a prescribing error for a patient switched from ACTIQ to FENTORA (section 5.5.3), and the 2nd report involved a dispensing error (section 5.5.2). In both cases a mcg-to-mcg conversion was noted.

Interventions

- In March 2007, Cephalon employed the addition of an in-line checkweigher into the manufacturing and packing process that verifies that a carton is within an established weight range. The goal of this intervention was to ensure that all blister cards and

package inserts/medication guides were contained in the carton. Any carton outside the weight range was rejected off the line. Upon review of all product complaints received for FENTORA, all reports involving loss of product involved batches packaged prior to this corrective action.

- With regard to the prescribing error noted above, Cephalon's Global Pharmacovigilance & Epidemiology department contacted the area business manager responsible for the territory in which this physician prescribes and advised that the field representative should re-educate the physician regarding the appropriate dose algorithm for FENTORA. With regard to the dispensing error noted above, Cephalon's National Account Manager contacted the patient's insurance carrier to reinforce the RiskMAP messages and explained that, because of the higher bioavailability of fentanyl in FENTORA, patients cannot substitute ACTIQ on a mcg-per-mcg basis with FENTORA.
- The reports of diversion were investigated in accordance with Cephalon's SOPs.

FENTORA® Risk Minimization Action Plan, 3rd Quarterly Report, 1 April 2007 – 30 June 2007

Observations

- Data obtained were increasing and allowing for greater review and assessment of components of the FENTORA RiskMAP.
- Of the 381 reports received during the 3rd quarter reporting period with sufficient information to determine opioid tolerance, approximately 87% (332 of 381) involved patients who were considered opioid tolerant prior to starting FENTORA. Data obtained from syndicated 3rd-party national audit data, specifically the IMS LRx and the Electronic Medical Claims Switch database, indicated that 19.0% of prescriptions written for FENTORA were for patients with a medical history of cancer on the basis of ICD-9 diagnosis codes.
- Patient survey data indicated that the Medication Guide was received and found helpful by 90% of survey respondents.
- There was 1 spontaneous report of accidental exposure during the reporting period that involved an elderly 73-year-old female with a history of Alzheimer's disease who mistakenly ingested FENTORA that was prescribed to her son; this incident resolved without an adverse outcome (section 5.6).
- Three spontaneous reports of suspected diversion were seen, including 1 report of missing FENTORA tablets from a box dispensed to a consumer (no manufacturing cause could be identified, indicating that the tablets may have been removed from the box by a 3rd party), 1 report from a DEA investigator regarding possible altering of drug product (investigator did not return Cephalon's follow-up calls and no further information is available), and 1 report of diversion of unknown cause.
- No data obtained from the RADARS early warning system detected any signals warranting interventions at this time.
- Seven medication errors were reported during this reporting period and were promptly addressed (section 5.5). These medication errors involved 3 patients who received FENTORA via an incorrect dose route, 1 conversion error from ACTIQ to

FENTORA, 1 death due to accidental FENTORA overdose as the result of a dispensing error (section 5.3.2), 1 report of incorrect usage of FENTORA (patient accidentally ingested 1st dose instead of buccal use as directed), and 1 report of a dispensing error in which a pharmacist substituted FENTORA for ACTIQ and patient experienced lightheadedness.

Interventions

- Multiple instances of inquiries to the call center were received by Cephalon's Medical Services department. In response, additional education and retraining was provided.
- Interventions were employed as a result of 3 of the 7 medication errors, as follows: (1) Cephalon's Medical Services Department reinforced appropriate dosage and administration instructions to a consumer who called in and reported a medication error; (2) a Cephalon field representative followed up with a pharmacist who had in error dispensed FENTORA as a substitute for ACTIQ during the reporting period; the field representative reinforced that FENTORA is not a generic ACTIQ and that FENTORA must not be substituted for any other fentanyl products; (3) a series of interventions were initiated in response to the error that resulted in a fatal outcome, including a root cause analysis to better assess if reinforcement of dosage and administration instructions was satisfactory or if the instructions warranted a change in labeling; and 4) all educational and promotional materials were specifically reviewed to obtain greater prominence of the dosage and administration language.
- The reports of diversion were investigated in accordance with Cephalon's SOPs.

FENTORA® Risk Minimization Action Plan, 4th Quarterly Report, 1 July 2007 – 30 September 2007

Observations

- Data obtained through the 4th quarterly report were increasing and allowing for greater review and assessment of components of the FENTORA RiskMAP.
- Of 399 postmarketing reports received during the reporting period, there were 308 evaluable reports, of which 84% (259 of 308) involved patients who were opioid tolerant prior to starting FENTORA. Approximately 16% of the reports (49/308) involved patients who were classified as opioid nontolerant. Data obtained from syndicated 3rd-party national audit data, specifically the IMS LRx and the Electronic Medical Claims Switch database, indicated that 17.2% of prescriptions written for FENTORA were for patients with a medical history of cancer on the basis of ICD-9 diagnosis codes.
- There were 9 reports of medication errors during the reporting period (section 5.5.1): 4 were related to actual or potential errors in drug prescribing (section 5.5.3); 3 were classified as therapeutic errors (all received as a result of active surveillance of the American Association of Poison Control Center [AAPCC] database) (section 5.5.4); and 2 were related to errors by the patient, involving either the schedule of drug administration or incorrect route of drug administration (5.5.4).

- There was 1 report of drug abuse, received from the AAPCC, involving a patient who also ingested 3 other unidentified substances (sections 5.3.1 and 5.4).
- There were 11 reports of suspected diversion received during the reporting period, as follows: 1 report from a site participating in a Cephalon-sponsored clinical study reporting that drug was stolen, 1 report involving a consumer who reported that he shared 1 FENTORA tablet with a friend, and 9 reports of missing FENTORA tablets. There were no serious adverse events associated with any report of diversion.
- There were 3 reports of fatal outcome involving patients treated with FENTORA (section 5.3.2).
- One report of a life-threatening event was received (section 5.3.3). Cephalon submitted 15 initial 15-day alert reports under the RiskMAP for FENTORA during this reporting period.

Interventions

- Regarding the 3 deaths, the Cephalon cross-functional response team immediately reviewed the cases and applied systematic follow-up in efforts to obtain additional information about each case. Cephalon learned that the events were predominantly due to inappropriate patient selection and medication prescribing errors.
- The combination of these events resulted in Cephalon's implementation of a series of interventions, including generation and distribution of a Dear Healthcare Professional (HCP) Letter to prescribers and other HCPs informing them of the serious adverse events, including deaths, that occurred during this reporting period. In addition, proposed changes to the package insert (including the Boxed Warning, Indications and Usage, Contraindications, Precautions, Information for Patients and Caregivers, and Dosage and Administration), Medication Guide, and carton labeling and enhancements to the RiskMAP were proposed to the FDA. Following dissemination of the Dear HCP Letter, Cephalon field representatives initiated delivery of the safety information, including enhanced dosage and administration instructions, that was included in the Dear HCP Letter.
- In 7 of the 9 reports of missing FENTORA tablets, no manufacturing cause was identified; the remaining 2 reports pertain to the same patient, and the cause was outside of Cephalon's scope.

5.11 Conclusions From FENTORA Postmarketing Data

Ten postmarketing reports of events considered serious by regulatory criteria were received through 31 December 2007. As of the datalock point, 6 of these events had fatal outcomes. As of March 2008, 1 additional report of an event with a fatal outcome was received after the datalock point and is included here for completeness.

As with other potent opioids, the primary risk associated with the use of FENTORA is respiratory depression specifically in opioid-naïve individuals and in cases of intentional or unintentional overdose, which can be fatal. Four of the 7 fatalities and 1 life-threatening event observed during the postmarketing period were a result of this primary risk. Because of this, several enhancements were made to the USPI, Medication Guide, and FENTORA carton label. A Dear Health Care Professional letter was written

and distributed. In order to further mitigate this serious risk, enhancements to the RiskMAP (described in the sections that follow) have been implemented, with additional tools proposed.

Inappropriate dose conversion from ACTIQ to FENTORA has the potential to result in serious adverse events. Since the initial launch of FENTORA, medication errors related to the route of administration were received and, subsequently, Cephalon demonstrated that the buccal and sublingual routes of administration are bioequivalent. The tools of the FENTORA RiskMAP enable Cephalon to react relatively quickly to new findings and modify information as needed to help ensure that FENTORA is administered properly to the appropriate patient population and within the dosing recommendations as described in the USPI.

The other main risks of FENTORA are the risks of abuse and diversion. To date, data received from both active and passive surveillance and monitoring systems indicate that abuse or diversion is reported with low frequency in conjunction with FENTORA, with no signal sites identified through RADARS.

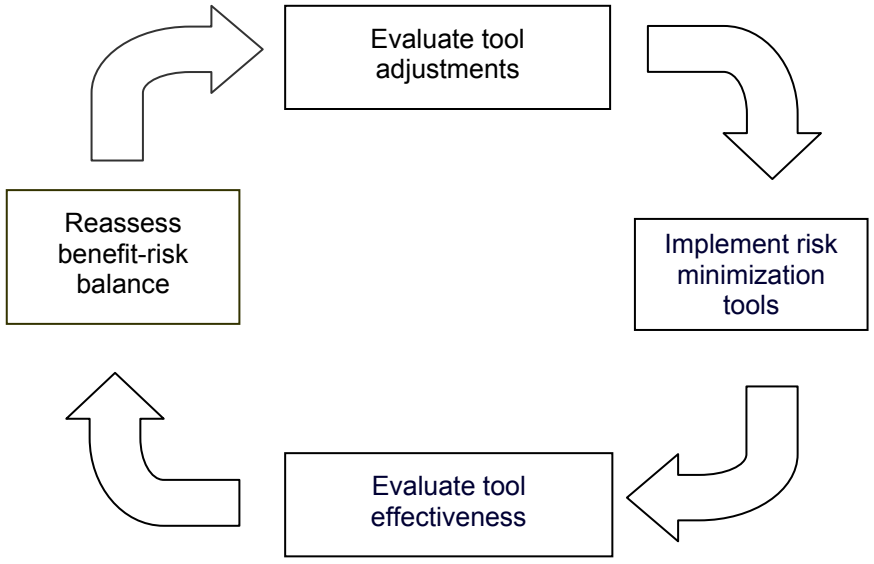
6 RISK MANAGEMENT FOR FENTORA

Risk management comprises an iterative process of assessing a product's benefit-risk balance, developing and implementing tools to minimize its risk while preserving benefits, evaluating tool effectiveness and reassessing the benefit-risk balance, and making adjustments, as appropriate, to risk minimization tools to further improve benefit-risk balance (FDA Guidance for Industry "Development and Use of Risk Minimization Action Plans"). The Prescription Drug User Fee Act IV (PDUFA IV) includes expanded counsel on risk management as described in the product's Risk Evaluation Mitigation Strategy (REMS). A principal component of the REMS is the Risk Minimization Action Plan (RiskMAP), which delineates implementation of risk management initiatives and comprises the following 4 elements:

- the methodology employed in identifying the risks associated with the product
- the measurable and actionable goals associated with each of the identified risks
- specific tools that will be implemented to minimize the risks
- an evaluation or feedback loop, whereby the sponsor prospectively defines metrics that will be employed in the RiskMAP to ascertain the effectiveness of the program

The process of benefit-risk management reflects a key principle of the RiskMAP (Figure 6-1). A RiskMAP generally cannot eliminate risks but is implemented to minimize risks while preserving patient benefits. Each RiskMAP goal has associated objectives, which should result in processes or behaviors to achieve the goals that should be specific and measurable.

Figure 6-1: The Process of Benefit-Risk Management



6.1 Cephalon Risk Management Experience

Cephalon has accumulated significant experience in the implementation and conduct of risk management programs (RMPs) for the opioid analgesic fentanyl with ACTIQ and FENTORA. ACTIQ is the 1st schedule II opioid analgesic that was introduced to the market with an RMP in 1998. Cephalon's risk management experience was continued with FENTORA, which was approved in September 2006 for the management of BTP in opioid tolerant patients with cancer. At this time, FDA guidance on risk management had incorporated the use of Risk Minimization Action Plans (RiskMAPs) in the risk management paradigm.

6.1.1 Experience With ACTIQ

ACTIQ was the first drug approved for management of BTP in opioid-tolerant patients with cancer. The active ingredient, fentanyl citrate, is a schedule II opioid with a known risk for abuse and diversion. The approved formulation of ACTIQ is a flavored, solid drug matrix on a handle, similar to a lollipop, and may pose an increased risk of pediatric accidental exposure, leading to the following risk minimization considerations:

- To reduce the risk of overdose, a definition was developed in collaboration with the FDA for "opioid tolerance," requiring an ATC opioid analgesic regimen for patients taking ACTIQ.[3]
- The information obtained during development of ACTIQ resulted in the first FDA-approved RMP for an opioid, addressing 3 key risks: accidental ingestion of ACTIQ by children, improper patient selection (ie, prescriptions to and usage by opioid-nontolerant patients), and diversion and abuse.
- To help ensure appropriate prescribing of ACTIQ, it was targeted to be used only in patients with cancer and only by oncologists and pain specialists knowledgeable of and skilled in use of schedule II opioids. A limited staged launch strategy was applied to mitigate against abuse and diversion and direct education to prescribers most knowledgeable in appropriate patient selection (specifically, opioid-tolerant patients).

Postmarketing data for ACTIQ indicate that risks were properly identified in the RMP and appropriate patient selection (ie, opioid tolerant), abuse rates, and rates of diversion occurred at acceptable levels to maintain an adequate benefit/risk ratio. It should be noted that a substantial proportion of the use of ACTIQ was outside the cancer population, ie, in opioid-tolerant patients with noncancer-related BTP.

6.1.2 Experience With FENTORA and Specific RiskMAP Interventions

6.1.2.1 Experience With FENTORA

FENTORA was approved in the US in September 2006 for the management of BTP in opioid-tolerant patients with cancer. The RiskMAP for FENTORA identified the same

[3] 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.

risks as were identified for ACTIQ. During the subsequent postmarketing observation period, surveillance and monitoring tools provided evidence for safety observations that were addressed following signal identification and evaluation. The process by which these safety observations were identified and addressed in the FENTORA RiskMAP, and a descriptions of the events, are summarized in the case study below. Additionally, a description of the evolvement of the tools from the ACTIQ RMP to the FENTORA RiskMAP is provided in Table 9-1 in the appendix.

Quarterly summaries of the postmarketing data that are relevant to the RiskMAP are provided in section 5.10.

6.1.2.2 Specific RiskMAP Interventions—Postmarketing Reports of Deaths and Medication Errors

As described above in section 5.3.3, a chain of events led to the most recent FENTORA labeling changes and inclusion of additional risk minimization tools to the approved FENTORA RiskMAP. This case study illustrates the iterative nature of the Cephalon FENTORA RiskMAP process and the company's immediate response to emerging safety and surveillance data.

(a) Description of Signal That Triggered the Changes

Cephalon received postmarketing reports of fatalities and medication errors during the period of June 2007 through August 2007 (Figure 6-2). The fatalities and life-threatening events were in patients who appeared to have been opioid nontolerant and should not have been prescribed FENTORA (section 5.3.2).

(b) Assessment of the Signal (Cephalon Risk Evaluation Algorithm)

Cephalon employs a risk evaluation algorithm that is applied for review of all events and determination of the appropriate interventions.

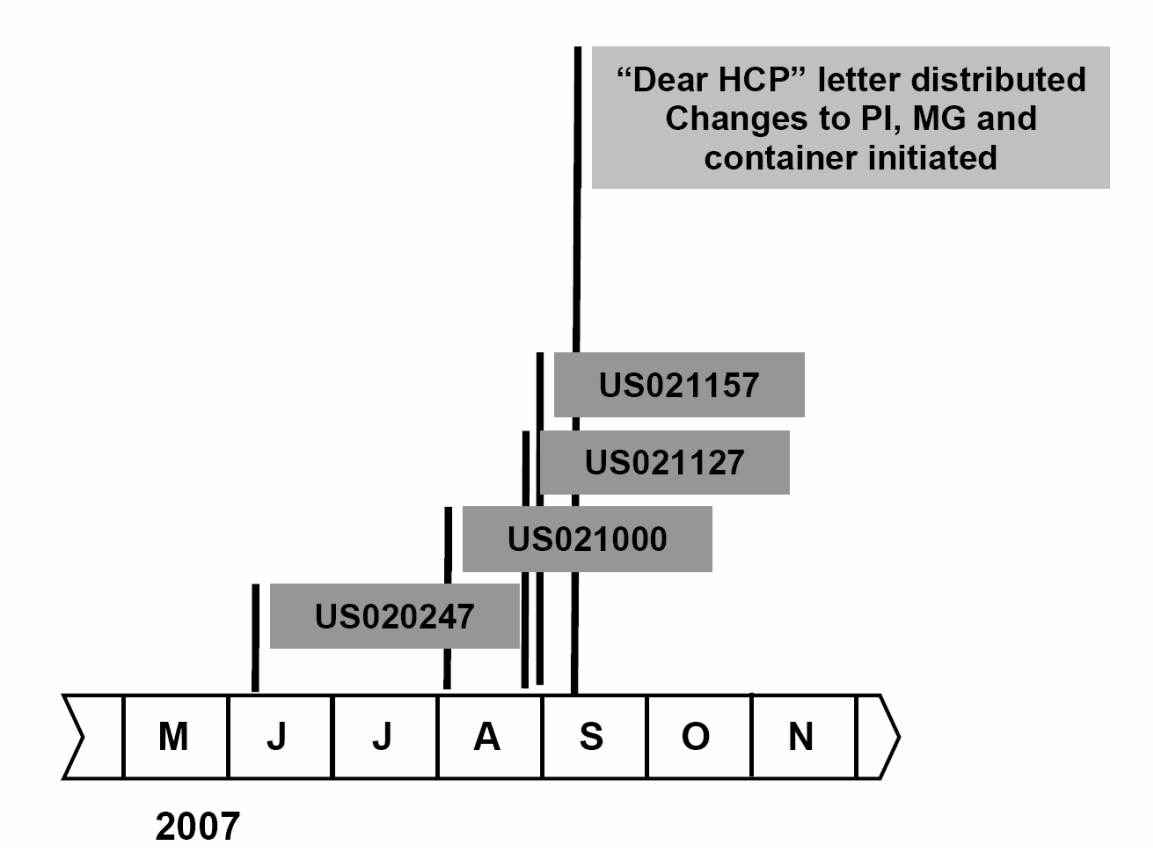
While the FDA was notified of the observed signal, the FENTORA safety group evaluated these reports, substantiated that the signal constituted a significant safety issue, and performed a root cause analysis, identifying the following 2 main causes associated with the reported events:

- lack of understanding associated with appropriate patient selection
- lack of understanding of the appropriate dosage and administration instructions, including conversion from other fentanyl products

Within days, Cephalon submitted a multiprong proposal to the FDA (Figure 6-2). Prompt interventions with regard to this proposal were as follows:

- a series of Dear Healthcare Professional letters to prescribers, pharmacists, and other healthcare professionals (HCPs)
- proposed (to the FDA) changes to the package insert, medication guide, and carton labeling

Figure 6-2: Cluster of Postmarketing Reports of Deaths and Life-Threatening Event: Timeline of Events



HCP=healthcare professional; PI=package insert (United States Package Insert); FDA=Food and Drug Administration; MG=Medical Guide.

Long-term solutions with regard to this proposal were as follows:

- a comprehensive educational initiative led by thought leaders in pain management, with goals of promoting best practices for identifying appropriate patient selection and prescribing of opioids
- additional interventions to the RiskMAP that Cephalon is initiating as a pilot to help address the need for greater education and safeguards at the patient and pharmacy levels, including adding a "safety debit card" to the patient kit and initiating a pharmacy real-time messaging program (Table 6-1)

Table 6-1: Description of Patient Kit and Pharmacy Real-Time Messaging Program

Intervention	Description
Safety debit card	◆Pilot program ◆To activate safety debit card, patients call toll-free phone number and hear safety messages about FENTORA, including how to appropriately dose and administer the product, maximum doses per day, and time interval between doses that must be employed for safe use. ◆This information will be heard by patient prior receiving FENTORA. ◆Real-time data will be available to Cephalon on patients who activated automated message system via the safety debit card and can then be monitored for outcomes. ◆Incentive to hear safety messages by small co-pay reduction if safety debit card activated.
Pharmacy real-time messaging program (notify Rx)	◆Computer-aided reminder system ◆Pop-up menu appears on computer screen each time a pharmacy accesses system to enter information on FENTORA. ◆Pharmacist is reminded to review with and disseminate to patient a medication guide and to provide reinforcing safety messages on appropriate administration before dispensing the product. ◆Pharmacist enters a random override code to acknowledge reading of the message and to complete the transaction. ◆Real-time data are available to Cephalon to monitor utilization of tool.

Rx=pharmacy.

(c) Changes Implemented

Changes that were made on the basis of these findings included the following:

- Dear HealthCare Professional letters, disseminated to approximately 30,000 HCPs on 11 September 2007
- a labeling supplement submitted to the FDA with modifications to the package insert, medication guide, and carton labeling; specifically, the package insert was revised in the following areas:
  - boxed warning
  - warning
  - precautions
  - contraindications
  - indication
  - information for patients and caregivers
  - dosage and administration
- Cephalon field force visited more than 4500 prescribing physicians and 1500 stocking pharmacies of FENTORA by mid-November 2007, reinforcing the messages that were also communicated in the Dear HealthCare Professional letter
- retraining of all speakers of the Cephalon Speakers Bureau by mid-November 2007 on the messages of the Dear HealthCare Professional letter
- updating of all Cephalon educational and promotional materials to incorporate the new information to help reinforce appropriate patient selection and understanding of how to safely dose and administer FENTORA

As is apparent from this example, Cephalon took the safety findings seriously and implemented an efficient and effective process to address emerging concerns in a timely and comprehensive manner. Essential to Cephalon's understanding of risk management is the continuous evaluation of tool effectiveness, surveillance data, benefit-risk balance and adjusting or adding tools as required to maximize the patient benefit while keeping risks at a minimum.

Although it is difficult to directly assess the impact of the above actions on the safe use of the product, it should be noted that as of completion of this document (4 April 2008), there have been no additional reports of death in opioid-nontolerant patients prescribed FENTORA.

6.2 Risks, Goals, and Objectives of the FENTORA RiskMAP for the Expanded Indication

The methodology used for identifying risks associated with FENTORA included the following:

- review of the known risks associated with the active pharmaceutical ingredient, fentanyl citrate
- the clinical study data obtained from the clinical development program with FENTORA and postmarketing data obtained for ACTIQ and FENTORA for the approved indication of BTP associated with chronic cancer-related pain
- an evaluation of the available information for the PALLADONE® (Purdue Pharma) RiskMAP program
- a failure mode effects analysis (FMEA), a prospective risk assessment methodology

Two primary risks were identified:

- Risk 1: Overdose with FENTORA
- Risk 2: Abuse and diversion of FENTORA

6.2.1 Risk 1: Overdose With FENTORA

In opioid-nontolerant patients, the risk of overdose is particularly prominent because comparatively low doses may cause symptoms of toxicity, such as respiratory depression. However, overdose can also occur in opioid-tolerant patients when the wrong starting dose is used, too many doses are used to treat an episode, or the medication is used too frequently throughout the day.

The primary root causes for overdose were identified as follows:

- use of FENTORA in opioid-nontolerant patients
- accidental exposure
- dosage and administration errors

Accordingly, the following 3 goals were specified to mitigate the risk of overdose:

Goal 1: FENTORA should be used only by opioid-tolerant patients

Goal 2: Unintended (accidental) exposure to FENTORA should not occur

Goal 3: Dosage and administration instructions should be provided to and understood by anyone who may prescribe, dispense, or use FENTORA

The corresponding objectives associated with these 3 goals are as follows:

- educate prescribers, pharmacists, and patients that FENTORA should be prescribed, dispensed to, and used only by opioid-tolerant patients
- reduce or mitigate potential for accidental exposure
- educate prescribers, pharmacists, and patients about "safe product use" to reduce or mitigate potential for accidental exposure
- educate prescribers, pharmacists, and patients about how to correctly dose and administer FENTORA to reduce potential overdose
- ensure the key messages regarding proper dosage and administration of FENTORA are provided prior to use

6.2.2 Risk 2: Abuse and Diversion of FENTORA

The second primary risk comprises the following key concerns:

- the risk of abuse in patients prescribed FENTORA
- the risk of diversion and subsequent abuse in patients not prescribed FENTORA

The following 2 goals were specified to mitigate this risk:

Goal 4: Abuse of FENTORA should not occur
Goal 5: Diversion of FENTORA should not occur

Objectives associated with these 2 goals are as follows:

- ensure adequate controls are instituted and maintained to prevent diversion of FENTORA from Cephalon's supply chain
- educate prescribers on appropriate patient selection to reduce risk of FENTORA abuse
- educate prescribers on the importance of providing proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage to reduce risk of abuse
- educate patients on the risk of diversion and how patients can mitigate this risk
- ensure adequate education, surveillance, and interventions are instituted and maintained to minimize diversion of FENTORA when the product is no longer within Cephalon's supply chain
- reduce potential abuse and diversion of FENTORA by providing education to healthcare personnel and pertinent nationwide demographic communities, performing ongoing surveillance of and targeted education/outreach to geographical outbreaks of abuse and diversion, and cooperating with and providing assistance to law enforcement in investigations of incidents of abuse or diversion

6.2.3 Points of Intervention

After identification of the risks, the FMEA included an assessment of possible points of intervention at which a break in the system could occur.

Six points of intervention were identified:

- supply chain
- prescribing
- dispensing
- consumer (patient) use
- storage of the product
- disposal of the product

Subsequently, the principal audiences that could be impacted at each of these points of intervention were identified:

- prescribers
- pharmacists and other HCPs
- patients (and caregivers)

Identification of the points of intervention and target audiences allowed Cephalon to select tools and interventions to specifically address each of the points of intervention and the respective target audiences. In addition, the tools were selected to accommodate the different learning strategies most commonly utilized, as follows:

- computer based initiatives,
- in person communications,
- print communications,
- continuing education and distance learning initiatives

6.3 Tools for Intervention

6.3.1 Staged Launch Strategy

Cephalon has developed a launch plan for the expanded indication, consistent with the launch plan employed upon initial approval for FENTORA in September 2006. The commercial strategy is to continue to provide education for safe and appropriate use to a concentrated universe of prescribers. Cephalon believes a principal component in mitigating abuse and diversion of FENTORA tablets is to employ a staged launch strategy.

6.3.1.1 Detailing to a Limited Number of Prescribers

Cephalon commits to continue to promote to the same number of prescribers (approximately 30,000) who were communicated with (approximately 17,000 targeted by field representatives) upon the initial approval of FENTORA. These physicians regularly prescribe both long-acting and pure short-acting opioids, and treat a significant number of the subgroup of patients with chronic pain and BTP for whom FENTORA would be indicated. For the first 18 months after approval of the expanded indication, data will be collected to measure the usage of FENTORA and ensure that the growth is managed. Cephalon will focus on the core prescribers to better understand what tools are most effective in mitigating the risks previously described.

Cephalon will also utilize information from this evaluation period to ensure it can adapt and readily modify plans as data increase. In addition to quarterly updates (see

section 6.5), Cephalon will provide the FDA with a RiskMAP assessment after 18 months to include any potential expansion or retraction of prescribers.

6.3.1.2 Identification of New Prescribers

Cephalon reviews prescribing data regularly to identify FENTORA prescribers; this information will be reconciled against the list of prescribers who have been visited by Cephalon's field force. If prescribers are identified outside of Cephalon-defined prescriber targets, a field force representative will attempt to visit them, convey key safety information, and provide all supporting educational materials. Cephalon will screen new prescribers for qualification to meet Cephalon's criteria of being skilled in the use of prescribing schedule II opioids. For prescribers not within this definition and where office visits by Cephalon's field force are not permitted (eg, surgeons), education will come from the corporate office to ensure new prescriber is educated and to maintain compliance with regarding Cephalon's sales and marketing practices.

6.3.1.3 Distribution to a Limited Number of Wholesalers

Similar to the detailing strategy, Cephalon employs a wholesaler distribution strategy whereby FENTORA is distributed by 22 wholesalers only. Each of the participating wholesalers must adhere to specific criteria and perform services according to Cephalon Criteria for Direct Account Agreement, including the following:

- must possess, among other licensure, a valid DEA license and demonstrate compliance with applicable laws and regulations governing distribution of pharmaceuticals
- must demonstrate that they have the capabilities to ensure supply chain integrity in accordance with Cephalon's RiskMAP

Cephalon evaluates wholesalers' purchases on a weekly basis and reviews data to identify any significant changes from week to week. Order lines may be cancelled if deemed appropriate.

6.3.2 RiskMAP Tools

The RiskMAP for FENTORA incorporates educational tools and interventions to achieve the goals associated with the identified risks and that leverage the points of intervention and principal audiences identified previously. There is intentional duplication of messaging and built-in redundancies to ensure coverage of the different target audiences and to accommodate the different learning strategies of individuals, such as computer-based initiatives, person communications, print communications, and continuing education and distance learning initiatives (Table 6-2). Detailed descriptions and purposes of the specific RiskMAP tools are provided in Table 9-1 in the appendix.

Table 6-2: RiskMAP Tools and Target Audiences

Origin of tool	Prescriber	Pharmacist	Patient (caregiver)
ACTIQ RMP	Medication guide (originally patient leaflet)	Medication guide (originally patient leaflet)	Medication guide (originally patient leaflet)
	Web site	Web site	Web site
	Educational introductory letter to healthcare professionals[a]	Educational introductory letter to healthcare professionals[a]	F1 blister
	Package insert	Package insert	Product returns and disposals
	Prescriber education	Pharmacist education	
	Independent continuing medical education	Independent continuing medical education	
		Carton label	Carton label
In addition, there is specific training for Cephalon field representatives, and reports of diversion and abuse from drug-diversion professionals.			
FENTORA RiskMAP (incorporating ACTIQ RMP)	Counseling aids (frequently asked questions)	Counseling aids (frequently asked questions)	Counseling aids (frequently asked questions)
	Patient kit with safety debit card	Patient kit with safety debit card	Patient kit with safety debit card
	Education to pain centers of excellence	"Pharm Alert"	Blister package label
	Education targeted to members of professional societies	Counseling messages (directed to pharmacy software)	Counseling messages (directed to pharmacy software)
	Pharmaceutical compendia	Pharmaceutical compendia	
		Notify Rx Messaging program	Notify Rx Messaging program

Abbreviations are at the end of the table. (continued)

Table 6-2: RiskMAP Tools and Target Audiences (Continued)

Origin of tool	Prescriber	Pharmacist	Patient (caregiver)
FENTORA RiskMAP for expanded indication (incorporating ACTIQ RMP and FENTORA cancer-related BTP tools)	RFID	RFID	RFID
	Electronic PEDIGREE (supply chain)	Electronic PEDIGREE (supply chain)	Electronic PEDIGREE (supply chain)
	RiskMAP core visual aid	RiskMAP core visual aid	RiskMAP core visual aid
	Resource folder	Resource folder	Catalina Newsletter
	Safety letter responding to reports of inappropriate patient selection and/or dosage	Safety letter responding to reports of inappropriate patient selection and/or dosage	
	Tamper-resistant prescription pads	Pharmacy checklist/stamp	
	Book on opioid prescribing	Auxiliary Rx labels	Auxiliary Rx labels
	Healthcare education (PROTECT)		
	Speakers programs		
	Speaker training		

[a] Includes the introductory letter and other communications to drug diversion authorities, which is directed to drug diversion professionals and addresses goals 4 and 5.
RMP=risk management program; RiskMAP=Risk Minimization Action Plan; PROTECT=Principles of Rational Opioid Therapy: Education, Communication & Translation; RFID=radio frequency identification; Rx=pharmacy; BTP=breakthrough pain; F1=requirements for child resistance and senior friendliness
.

6.3.3 Strategy and Tools Associated With Goal 1: FENTORA Should Be Used Only by Opioid Tolerant Patients

Considerable and renewed efforts have been put into preventing use of FENTORA in opioid-nontolerant patients to mitigate the risk of overdose. These renewed efforts include significant modification to tools currently employed in the FENTORA approved RiskMAP and the addition of new tools that Cephalon believes will reinforce the message that FENTORA should be used only by opioid-tolerant patients.

6.3.3.1 Prescriber/Healthcare Professional

The FENTORA product labeling was substantially enhanced from its initial approval and provides strong command language to the HCPs, alerting them to risks of use of this product and the importance of appropriate patient selection (opioid tolerant). A boxed warning informs the prescriber not to use FENTORA in the following:

- not to use FENTORA in opioid-nontolerant patients
- to distinguish between opioid exposed (PRN) and opioid-tolerant patients
- gives examples of patient populations at greater risk for being opioid nontolerant
- specifically delineates contraindicated population indications

A prescriber/HCP checklist will be employed to help aid prescribers in appropriate patient selection. The prescriber will go through a list of specific selection criteria to determine if the patient can be considered opioid tolerant (at least 60 mg of oral morphine/per day or equivalent) at the time of and after initiating use with FENTORA. Command language directs the prescriber not to prescribe FENTORA if he or she learns from this exercise that the patient is not opioid tolerant.

Other targeted education and outreach directed toward prescribers includes the following:

- introductory letters
- visits and assessments by Cephalon field representatives
- educational programs specific to Pain Centers of Excellence, professional societies, and those prescribers specializing in pain management (PROTECT)
- book on appropriate prescribing of opioids authored by key opinion leaders in the field of pain management, including diagnostic tools to aid the prescriber with appropriate patient selection
- resource folder comprised of current literature to aid prescribers in appropriate patient selection
- the PROTECT Program, a comprehensive educational initiative sponsored by Cephalon, was developed by key opinion leaders for delivery to medical audiences. Programs will focus on appropriate prescribing of opioids and identification of appropriate patient selection. Programs will be delivered by various means including face-to-face lecture series, webinars, CD-ROMs, teleconferences, and written materials to support the different manners in which professionals learn.
- Cephalon supported continuing medical education (CME) to further the education of prescribers to enhance their understanding of appropriate patient selection for use with opioids and best practices for pain management (NOTE: CME programs will be conducted in accordance with FDA and ACCME guidelines).
- Cephalon Speaker Programs (CSPs) with speakers fully trained on the FENTORA RiskMAP will be provided with a standard slide kit to educate other HCPs on the RiskMAP, as follows:
  - a branded CSP to provide education highlighting the risks and benefits specifically of FENTORA, particularly how to mitigate risk of overdose
  - a nonbranded CSP to educate prescribers about the risks of abuse and diversion with schedule II opioids and how to mitigate such risks in clinical practice.
- RiskMAP core visual aids will help the prescriber in appropriate patient selection in mitigating risks for overdose and abuse and diversion. This core visual aid incorporates a patient tear-away sheet that fully describes the risk of overdose with use of FENTORA, describes how this risk may be mitigated through appropriate patient selection (ie, must be opioid tolerant, must not be at risk of accidental exposure or misuse and abuse), and highlights dosage and administration guidelines.

- The FENTORA professional web site, which will have a dedicated area for SECURE, will be a venue where prescribers can access information at any time on safe use for FENTORA and can learn more about appropriate prescribing of opioids and patient selection.

6.3.3.2 Pharmacist

Tools directed toward pharmacists will also include introductory letters and visits by Cephalon field representatives. Counseling messages targeted to the pharmacist will be distributed to pharmacies by major publishers of pharmacy counseling software and will also be conveyed to pharmacies via newsletters, emails, and web-based media.

The packaging of FENTORA provides an opportunity to employ use of reminder messages prior to the point of dispensing. Included on the carton are the following:

- The pharmacist checklist, which was initially conceived with ACTIQ and employed with FENTORA since its initial approval, but was recently enhanced. Enhancements to the Pharmacist Checklist include the following:
  - warnings that when dispensing, never substitute FENTORA with another fentanyl product
  - reminders to review the prescription with regard to dosing because patients switching to FENTORA from another fentanyl product should not be converted on a mcg-per-mcg basis
- The familiar inverted triangle, also initially conceived with ACTIQ and included with the initial development of FENTORA, will be placed on the outer carton next to the warning to keep out of the reach for children and that patients must be opioid tolerant (NOTE: This warning will be displayed on multiple panels of the carton).

New tools included with this iteration of the RiskMAP to prompt the pharmacist at the point of dispensing to make certain that a patient is opioid tolerant include the following:

- duplicative reminder pharmacist checklist in the format of pad, sticker, and/or stamp
- auxiliary labels affixed to the carton
- a computer facilitated pop-up system (Notify Rx pilot program)

6.3.3.3 Patient

Patient education will rely on information specifically designed for patients and written in consumer-friendly language. Patient tools currently included with the FENTORA RiskMAP that were enhanced with this iteration include the following:

- medication guide that describes the serious risks associated with FENTORA and how to safely use FENTORA to minimize an occurrence of such risks
  - the medication guide explains that life-threatening breathing problems can occur if FENTORA is taken by anyone who is not already taking other opioid pain medicines (ie, not opioid tolerant)
  - the medication guide was enhanced to include stronger language regarding a description of who should never take FENTORA, instructions for when to stop taking FENTORA, what to do when observing signs or symptoms of a serious adverse event, and instructions regarding safeguarding of the product

- a web site with a patient-friendly entry portal allowing patients to obtain information about the safe use of FENTORA

Significant efforts have been made to increase patient education, recognizing that the prescriber and pharmacist may not always provide adequate time to appropriately educate the patient on the safe use of the product at the point of prescribing and dispensing, respectively. Hence, by increasing the education targeted to the patient directly, Cephalon believes a well-educated patient may help to mitigate the risk of overdose. Additional tools included in this iteration of the RiskMAP are as follows:

- patient tear-sheet, intended to complement the medication guide, will be disseminated by prescriber at time of providing patient with the prescription. The tear-sheet will articulate the appropriate patient selection for FENTORA, proper dosage and administration instructions, and how to store and dispose of FENTORA.
- auxiliary pharmacy labels affixed to the carton intended to provide the patient with another reminder of how to safely use FENTORA
- a newsletter (Catalina Newsletter) attached to each prescription will include important dosing instructions
- patient kit, including a patient use demonstration video, frequently asked questions (FAQ) brochure, placebo pack to aid the patient in practicing administration of the buccal tablet prior to use of the actual medication, caregivers' brochure, pain diary, and safety debit card system (which is currently being piloted)
  - during the pilot, a predefined sample of patients will receive a patient kit containing the safety debit card offering discounts to the patient's co-pay after receiving important safety information about FENTORA
  - to activate the card, patients must listen to important safety messages, including instructions for dosage and administration, prior to receipt of FENTORA

Significant modifications have been incorporated into all patient materials with regard to the dosing algorithm for FENTORA. Dosing instructions have been segmented into 1) initial dose, 2) titration dose, and 3) maintenance dose to provide the patient with the simplest but most thorough way of ensuring proper administration of FENTORA.

6.3.4 Strategy and Tools Associated with Goal 2: Unintended (Accidental) Exposure to FENTORA Should Not Occur

Accidental exposure to FENTORA may lead to overdose symptoms with potentially fatal consequences and must be minimized. The physical characteristics of this formulation, coupled with postmarketing data obtained since the launch of FENTORA (only 1 report of accidental exposure), suggest a reduced risk of pediatric accidental exposure compared with ACTIQ.

Principal tools pertinent to Goal 2 include the following:

- all labeling components associated with FENTORA
  - blister, which meets F1 requirements for child resistance and senior friendliness
  - blister label, which contains a warning intended to mitigate risk of overdose

  - carton label, which contains warnings including "FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA"
  - medication guide and package insert, with specific warnings
- product returns and disposals process to enable patients to return unwanted FENTORA in an appropriate manner

Furthermore, all of the tools previously described for Goal 1 also include appropriate messaging regarding the risk of accidental exposure and, therefore, are intended to meet the objectives of Goal 2.

6.3.5 Strategy and Tools Associated With Goal 3: Dosage and Administration Instructions Should Be Provided to and Understood by Anyone Who May Prescribe, Dispense, or Use FENTORA

The dosing paradigm for FENTORA is complex, warranting multiple tools to ensure that instructions are provided to anyone who may prescribe, dispense, or use FENTORA and, more importantly, that audiences understand how to properly select doses for FENTORA.

As previously discussed in section 6.3.3.1, patient education begins with the prescriber. Cephalon will distribute placebo blister packages to prescribers to help facilitate discussions between prescriber and patient, whereby they are demonstrating safe administration of the tablet.

After the patient obtains a prescription, pharmacist counseling is intended to reinforce the prescriber's directions. As previously noted, Cephalon is employing a pilot program (patient kit containing a safety debit card) to aid the patient in obtaining important dosing and other safety information about FENTORA prior to the point of dispensing. Because pharmacist counseling may not consistently occur, this card will provide another point of intervention to ensure patients are getting the necessary information before they receive the medicine (section 6.3.3.3). Additionally, the patient will have a medication guide accompanying every prescription that will reinforce the appropriate patient selection and dosage and administration instructions. When the prescription is filled, the pharmacist will counsel the patient again on the appropriate dosage and administration instructions accompanying the prescription and the important safety reminders regarding the maximum doses that may be taken and the interval of time to wait between doses.

After the patient receives FENTORA from the pharmacist, the outer carton labeling is intended to provide important warning language. The carton contains an inverted triangle symbol in multiple panels, which now is recognized by patients as a means of conveying important warning information. The symbol, in conjunction with the boxed warning, increases the perceived importance of the warning message to keep the product out of the reach of children. It has become associated with the importance of safe storage and use and disposal in packaging materials directed to patients (section 6.3.3.2).

Physicians and pharmacists will be provided with the patient tear-sheet to increase the likelihood of ensuring provision and receipt of these important messages and to utilize different venues to facilitate discussion between the patient and HCP.

6.3.6 Strategy and Tools Associated With Goals 4 and 5: Abuse of FENTORA Should Not Occur and Diversion of FENTORA Should Not Occur

A number of tools were developed to reduce risks of a potential increase in diversion or abuse with increased usage through reinforcing understanding of proper control of shipping and distribution, proper prescribing, proper dispensing of initial prescriptions and refills, and control of returned or unused medication. Strategies include the following:

- Cephalon will track every shipment of FENTORA from its manufacturing sites to its receipt at the wholesaler.
- Drug accountability will be maintained to ensure diversion has not occurred from the time the product departs Cephalon to when it is received by the wholesaler.
- As part of Cephalon's existing SOP, wholesalers who purchase product from Cephalon must verify that they have processes and procedures in place to minimize the risk of diversion when the product is received by the pharmacies (prior to Cephalon release of product).

To address abuse within the prescribed population, Cephalon enhanced its previous tools to provide greater aid to the prescriber for appropriate patient selection and to identify aberrant behaviors that may indicate and increased potential for abuse, as follows:

- The FENTORA labeling components (carton label, medication guide, and package insert) have specific sections dedicated to aid with appropriate patient selection. The package insert warns of populations at greater risk for aberrant drug behaviors and cautions the prescriber when considering using FENTORA in such populations.
- Introductory letters directed to HCPs, pain centers of excellence, and professional medical societies will be disseminated at the time of launch of the new indication to provide immediate awareness of the product's new use and safety information to minimize the potential for abuse in the patient population.
- The CME program, Emerging Solutions in Pain (ESP), as a tool to help reduce abuse and diversion. This tool kit is comprised of various educational components directed to foster the following:
  - comprehensive prescriber education on appropriate patient selection
  - identification of aberrant or drug seeking behaviors
  - screening tests to employ when considering starting a patient on opioids
  - technique to monitor patients once prescribed an opioid

Additional tools included in this iteration of the RiskMAP to minimize an increase in abuse and diversion include the following:

- CSPs dedicated to educating HCPs on abuse, addiction, and diversion will be conducted prior to launch of the expanded indication and at the time of and through the life of product.

Pharmacists will be informed to exercise caution when dispensing FENTORA to patients and will be educated about aberrant behaviors to help them reduce risk of diversion at the pharmacy level. Face-to-face and written educational interventions for the pharmacist will be comparable to those described for the prescriber. As previously discussed, Cephalon is currently piloting a computer-aided pharmacy level intervention (Notify Rx)

(section 6.3.3.2). Messaging in this program can be utilized to help aid pharmacists in recognizing aberrant behaviors and/or reminding the pharmacist to counsel the patient regarding safeguards to employ to minimize risk for diversion after receiving FENTORA.

To further safeguard supply integrity to reduce potential diversions, Cephalon will be prepared to employ use of radio frequency identification (RFID) technology and electronic drug pedigree (PEDIGREE), in accordance with pertinent state legislation, to monitor the chain of custody. These tools have been identified as having great potential to the pharmaceutical industry in helping to reduce diversion; however, the ability to implement these tools and determine their value are currently limited by a lack of available hardware applications (ie, RFID readers) in distribution centers and pharmacies.

The safety debit card program currently being piloted (section 6.3.3.3) also offers the possibility to more closely monitor the chain of custody because Cephalon can have access to real-time data for every patient employing use of the card at the dispensing pharmacy.

6.4 Surveillance and Monitoring

With the approval of the initial NDA, Cephalon identified a series of surveillance and monitoring systems to evaluate effectiveness of RiskMAP tools. These systems include surveys of the prescribers, pharmacists, and patients; surveillance systems; national prescription audit data (ie, IMS); other surveillance activities; and Cephalon pharmacovigilance. All of these will continue with the enhanced RiskMAP.

6.4.1 Surveys

Three surveys targeted to each of the 3 primary audiences, prescriber, pharmacist, and patient, were developed to measure knowledge, attitude, and behaviors associated with the FENTORA RiskMAP. All surveys are administered to the respective audiences via telephone. Detailed descriptions of the surveys are provided in (Table 9-2 in the appendix).

6.4.2 Surveillance Systems

Monitoring of national audit data are used to track specific outcomes related to abuse and misuse. Cephalon uses the American Association of Poison Control Centers (AAPCC; formerly Toxic Exposure Surveillance System [TESS]) exposure database and the US Department of Health and Human Services Drug Abuse Warning Network (DAWN) to augment routine pharmacovigilance activities. However, there are significant time lags associated with the above systems. Therefore, Cephalon has also incorporated active surveillance and monitoring systems into its RiskMAP, including Denver Health's Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System and the DAWN Live! These surveillance systems are described above in sections 5.8.1 and 5.8.2 and in Table 9-3 in the appendix.

6.4.3 Review of Prescription Audit Data

Cephalon is reviewing prescription audit data, such as the IMS National Prescription Audit (NPA) Plus Database that captures the volume of prescriptions dispensed from retail, mail service, and long-term care channels, and medical claims data, such as the IMS Medical Claims Switch (MCS) Database that captures a portion of claims submitted by physician offices and facilities. Information for FENTORA extracted from these databases may be used to evaluate use of FENTORA by patients with cancer and other diagnoses.

Cephalon purchases longitudinal data, specifically the IMS Longitudinal Prescription Database (LRx) to help assess the degree to which FENTORA is prescribed to patients who have a recent prescription for another opioid medication. With these data, Cephalon can determine if an additional opioid medication was prescribed/dispensed in the month or previous months prior to the FENTORA prescription. Cephalon looks at these data to help assess the indication for which FENTORA was used.

As with any national audit data, there are limitations, and caution should be exercised when trying to draw conclusions. Limitations of IMS data are as follows:

- IMS NPA data are projected from a sample of prescriptions; therefore, higher error ranges are associated with lower volume products. This must be taken into account when interpreting the information.
- The IMS Longitudinal Database (LRx) captures only a portion (50%) of prescriptions from the retail segment and may miss prior opioid prescriptions filled at "out of sample" outlets—nonparticipating retail outlets, long-term care facilities, hospitals or mail order.
- The IMS Medical Claims Switch Database (MCS) does not capture prescription data so IMS cannot actually discern what the prescription was written for, but for a segment of patients (about 45% of patients in the longitudinal database), IMS can identify the associated diagnoses of patients prescribed FENTORA.

6.4.4 Other Surveillance Activities

Cephalon routinely monitors media from remote small-town rural areas of the country to metropolitan cities, enabling identification of any potential abuse or diversion signal developing that warrants intervention.

6.4.5 Cephalon Pharmacovigilance

All spontaneously reported adverse events are captured in the Cephalon safety database (see also section 5.2). In addition, all Cephalon personnel are trained to forward adverse event reports immediately to Cephalon's Global Pharmacovigilance & Epidemiology department. Cephalon's Postmarketing Surveillance and Pharmacovigilance activities include the following:

- collection and evaluation of postmarketing adverse events

- reports related to overdose, abuse, or misuse with FENTORA
- all actual and potential medication errors associated with use of FENTORA

6.5 Signal Detection and Evaluation

Trends will be identified and compared by quarter using data observed in quarterly intervals. Additional comparisons will be performed with time frames varied as appropriate to allow evaluations between time periods prior to supplemental NDA approval. Cephalon will provide the FDA with data on a quarterly basis (see section 5.10 for review of previous reports).

Quarterly updates will include systematic evaluations regarding the following:

- extent of use (denominator estimates)
- indicators of inappropriate prescribing (ie, opioid-nontolerant patients) inclusive of patient longitudinal data
- summarization of reports involving all medication errors, regardless of patient outcome
- summarization of all accidental exposures
- summarization of all nonaccidental pediatric exposures
- summarization of adverse events involving opioid-nontolerant patients
- rates of suspected misuse, abuse, addiction, or diversion reported
- results of any surveys conducted
- results of any investigations conducted
- outcomes from regional or otherwise targeted interventions, such as targeted educational interventions and antidiversion programs conducted

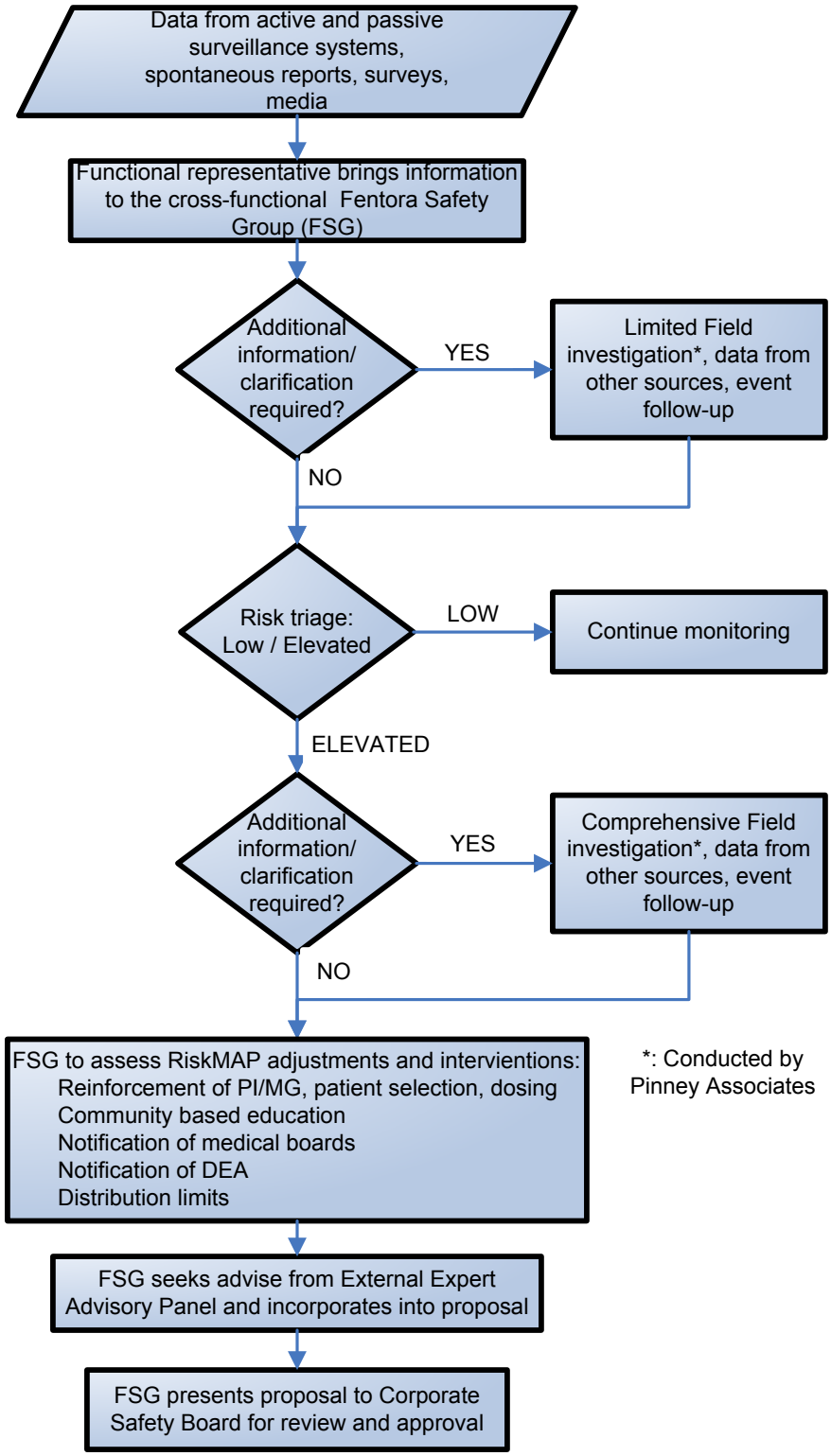
Additionally, for identifying and reporting signal detection, the following processes will be used:

- Reporting will be evaluated separately for spontaneous reports and other reports derived from the AAPCC and Drug Abuse Warning Network (DAWN) data.
- With data provided in the RADARS report, Cephalon will identify signals using the current signal thresholds recommended by the RADARS Scientific Advisory Board as determined for both rates per 100,000 population and rates per Unique Recipient of Dispensed Drug (URDD). Since distribution of FENTORA is relatively low and very few reports are received for FENTORA, Cephalon will consider, in addition to quantitative thresholds, qualitative criteria for signal identification. Thus, any report from data from RADARS will be evaluated and possibly followed by a field investigation.
- Emerging signals will immediately be evaluated by the Cephalon FENTORA safety group following a process established with the RiskMAP (Figure 6-3). The Cephalon signal evaluation and decision process enables the FENTORA Safety Group to quickly assess emerging signals, decide on additional information required, and escalate issues immediately to make a decision. As noted above, distribution of FENTORA is relatively low and very few reports are received for FENTORA; therefore, Cephalon is not assigning a quantitative threshold for signal determination to serious adverse events but will review every event of overdose, accidental exposure, and other important medical events for emerging signals.

For signal evaluation, the following assessments will be used:

- A field investigation can include a telephone interview or a face-to-face meeting with the primary reporter or someone with direct knowledge regarding the event.
- Contacts may include, but are not limited to, law enforcement officers, school officials, and substance abuse treatment program administrators.
- The information retrieved from this contact will be limited by the willingness and spirit of cooperation of the individual contacted, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and other privacy protection acts.
- In addition, for comparative purposes, reporting rates will be compared to those of ACTIQ and to that of FENTORA during the 1st year of marketing.
- Cephalon employs the expertise of external consultants to review the RiskMAP at least twice a year.

Figure 6-3: Cephalon Signal Evaluation and Decision Process for Tool Adjustments



PI=package insert; MG=Medication Guide

6.6 Conclusion

Over the past decade, Cephalon has accumulated extensive experience in the management of risks associated with opioid analgesic drugs, specifically fentanyl.

Cephalon has established a comprehensive and effective risk management process consisting of risk minimization tools and strategies, metrics to measure tool effectiveness, continuous benefit risk balance evaluation and tool adjustments or replacements as needed. Cephalon views the risk management program as an iterative process for the life of the product, a continuous cycle of interventions, metrics, assessments and adjustments. Cephalon will adapt and incorporate any necessary modifications to the RiskMAP as data accumulates and knowledge increases, as it has done successfully with the existing RiskMAP.

The tools selected for the FENTORA RiskMAP are selected based on Cephalon's experience and were further developed and refined as surveillance data accumulated and safety signals were generated. The tools systematically cover all points of intervention identified during the FMEA analysis and provide an intentional redundancy and duplication of messaging to 3 identified target audiences (prescribers, pharmacists, and patients), accommodating all major modalities of educational activities, including computer-based initiatives, in-person communications, print communications, and continuing education and distance learning initiatives. Cephalon continues to develop new tools to increase the effectiveness of the RiskMAP and has multiple pilot initiatives currently under evaluation.

Cephalon will commit to a staged launch strategy whereby Cephalon will not expand its detailing effort beyond the current prescriber target of 4% of all prescribers with a DEA registration to prescribe schedule II drugs. Any actual FENTORA prescribers not in this target list will be contacted by Cephalon to ensure receipt of the important safety messages. This will be reassessed after an 18-month period.

Cephalon has acquired the ability to manage the risks associated with FENTORA to keep them at tolerable minimum, thus allowing patients the needed benefits of this novel fentanyl formulation.

7 BENEFIT/RISK

There is an unmet need for better management of BTP in opioid-tolerant patients with moderate to severe chronic pain. The fear of BTP episodes and inadequate treatment in the outpatient setting can have significant consequences for this subgroup of patients with chronic pain. The benefits of treatment with FENTORA have been previously demonstrated in studies in opioid-tolerant patients with cancer-related pain and BTP; however, these patients represent only a portion of the chronic pain population that could benefit from FENTORA treatment. This is reflected in the use of fentanyl-containing products to treat patients with severe chronic cancer-related pain.

The tablet formulation of FENTORA can be easily administered buccally, and if needed it can be administered sublingually. Studies with FENTORA have shown that on average, 80% of the maximum plasma concentration of fentanyl is achieved within 25 minutes of tablet placement, and this concentration is maintained through 2 hours—characteristics desired in a medication intended for a condition such as BTP. Across all clinical efficacy studies, statistically significant differences observed with FENTORA compared with placebo in pain intensity and pain relief scores begin to consistently emerge within 30 minutes, often in less than 15 minutes, another characteristic clearly important in a condition where the peak pain intensity is often reached within minutes from the onset of the BTP episode. These differences were clinically meaningful. The analgesic effects observed with FENTORA treatment were consistently observed in all demographic groups and with all types of BTP, whether predominantly neuropathic, predominantly nociceptive, or mixed (approximately 50% neuropathic, 50% nociceptive).

With regard to the adverse event profile of FENTORA, the most common adverse events observed were characteristic of those associated with fentanyl and other opioids. The safety and tolerability profile of FENTORA observed in opioid-tolerant patients with chronic noncancer-related pain and BTP was similar to that seen in the studies involving opioid-tolerant patients with cancer.

Overdose resulting in respiratory depression, which can be fatal, is a known risk associated with opioids, and a number of actions must be taken to mitigate this risk. Appropriate patient selection is very important in mitigating the risk for unintended overdose. Thus, FENTORA is contraindicated in patients not already opioid tolerant. In addition, patients at significant risk for suicide or with a history of opioid abuse and addiction should not be prescribed FENTORA. Once appropriate patients are selected, limitations must be placed upon dosage. Specifically, patients should be dispensed only 1 dose strength at a time in order to prevent dosage errors. Patients must be instructed to take no more than 2 tablets per BTP episode (at least 30 minutes apart), wait at least 4 hours between episodes, and not to treat more than 6 episodes in a day. Patients should be warned that consumption of alcohol or other central nervous system (CNS) depressants except those prescribed for the patient may potentiate the CNS-depressant effects of FENTORA and ATC opioids. By repeated consistent communication of these instructions to physicians, pharmacists, and patients, the risk of overdose can be reduced.

Like other drugs of its class, FENTORA may be habit forming and has the potential for abuse and diversion. Safe use of FENTORA requires careful selection and management of patients by the physician. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or severe mental illness (eg, psychosis, mania, bipolar disorder, or schizophrenia). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed FENTORA. All patients receiving FENTORA should be routinely monitored for signs of misuse, abuse, and addiction, including the identification of aberrant drug-use behaviors. This may include regular urine drug screening.

In conclusion, treatment with FENTORA has been shown to be effective in opioid-tolerant patients with chronic pain and BTP with an acceptable safety profile, and the risks seen with FENTORA are characteristic of those associated with fentanyl and other opioids. The most significant of these risks are overdose, abuse, and diversion. With the expansion of the indication beyond opioid-tolerant patients with cancer-related BTP, Cephalon has developed an enhanced and comprehensive RiskMAP to keep these risks at a minimum. There is currently no FDA-approved medication for the treatment of opioid-tolerant patients with BTP associated with chronic noncancer-related pain. With appropriate patient selection, clear instructions on dosage and administration, and careful monitoring, FENTORA represents an important treatment for opioid-tolerant patients with chronic pain and BTP.

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9 APPENDIX

9.1 Brief Descriptions of Serious Adverse Events of Overdose

Ten patients had serious adverse events associated with opioid overdose while participating in a clinical study of FENTORA. The following are brief narrative descriptions with regard to these adverse events:

- Patient 003021 (study 3040), a 47-year-old woman, titrated study drug to a successful dose of 800 mcg on day 8. On day 11 during the maintenance treatment period, she experienced serious adverse events of severe respiratory failure and severe unresponsiveness to pain stimuli. The patient was reported as having taken six 800-mcg tablets of FENTORA over an 11-hour period (data on file). The patient's daughter found her unconscious and cyanotic with agonal respirations; the patient was intubated by emergency medical services, transported to the hospital, and placed on a ventilator for respiratory failure. Serum toxicology test results were positive for benzodiazepines and barbiturates. A significant quantity of spirit alcohol was noted in the vicinity where the patient collapsed. The events resolved with no residual effect on day 15 and the patient was withdrawn from the study.
- Patient 019004 (study 3040), a 47-year-old white man with chronic back pain, was receiving oral morphine at 90 mg daily as ATC medication and FENTORA at 800 mcg as needed for BTP in study 3040. He was also taking valproate semisodium for migraine headaches. On day 341, he was admitted to the hospital after attempting suicide, reportedly via an intentional overdose of pain medication (unspecified). The patient was discharged from the hospital and the next day (day 345) he again attempted suicide, this time taking valproate and other non-opiate medications. He was withdrawn from the study.
- Patient 019010 (study 3040), a 67-year-old white woman, reported an intentional multiple drug overdose (methadone and lorazepam), suicide attempt, and acute psychosis on approximately day 490 of the maintenance period. The events resolved and were considered by the investigator not related to treatment with the study drug.
- Patient 025003 (study 3040), a 54-year-old white woman with chronic back pain, experienced serious adverse events of severe mental status changes subsequent to falling and hitting her head and accidental overdose on day 131. These serious adverse events resolved on day 140 and the patient was subsequently withdrawn from the study. The patient's last recorded dose of study drug was on day 123. The investigator considered these events not related to study drug.
- Patient 026010 (study 3040), a 63-year-old white woman with osteoarthritis, spinal stenosis, and peripheral neuropathy who had been using the 200 mcg tablet of FENTORA for BTP, reported severe lethargy, listlessness, and change in mental status on day 99. She was taken to the emergency room and treated with naloxone, to which she responded. However, 1.5 hours later she became somnolent and less arousable. Patient reported that her doxepin for sleep had been changed to amitriptyline 2 weeks prior to the event. The patient's dose of methadone was

reduced from 40 mg 3 times a day to 30 mg 3 times a day and she continued in the study.

- Patient 030008 (study 3040), a 45-year-old white woman with chronic low back pain (predominantly nociceptive), was using methadone for chronic pain and OXYCOCET® as rescue medication. The patient was using 800 mcg of study drug to treat her BTP episodes. On day 601, her husband found her somnolent and difficult to awaken. She was taken to the emergency room and treated with naloxone hydrochloride and glucagon. It was determined that after awakening from a morning nap, the patient took her morning medications ([FLEXERIL®, atenolol, LIORESAL®, KLONOPIN®, and methadone) a second time by accident. The adverse event of accidental overdose was considered resolved with no residual effect on the same day, day 602. The patient completed the study and took her last dose of study drug on day 629.
- Patient 511003 (study 3040), a 54-year-old white woman with chronic back pain, had 2 adverse events of unresponsiveness to stimuli. Approximately 10 months after the start of FENTORA treatment, this patient was visiting her mother and had an episode of unresponsiveness following the ingestion of one 800-mcg tablet of FENTORA. She was transported to the hospital, treated with naloxone, and the event resolved on the same day. This event was not reported to the investigator at the time it happened. Ten days after the first event, the patient experienced a second event of unresponsiveness (initially reported as overdose). The investigator felt that the oxycodone and cyclobenzaprine also contributed to the event, and that the patient was unreliable. The patient was withdrawn from the study on day 303 due to the serious adverse events.
- Patient 513017 (study 3040), a 54-year-old black man with chronic back pain who entered study 3040 after participating in study 3042, was receiving a successful dose of 800 mcg of FENTORA. On day 52, he experienced a serious adverse event of unresponsiveness and respiratory distress secondary to an accidental overdose. The patient received naloxone. The patient later reported that the last dose of study drug taken was at approximately 1600 (4 pm) that same day. It is not known when the patient took his doses of ATC opioid, oxycodone. The patient was withdrawn from the study because of these adverse events.
- Patient 503003 (study 3042), a 60-year-old white man with chronic back pain, reported taking 4 tablets of study drug on day 6, which he believed to be the 100-mcg dose strength. His wife found him unresponsive. Paramedics revived him with oxygen and he was taken to an emergency room. This was reported as an accidental overdose; drug accountability records indicated that he took 4 tablets of the 600-mcg dose strength. The patient was withdrawn from the study on day 7 due to these events.
- Patient 026008 (study 3052), a 53-year-old white woman, had back and leg pain due to multiple sclerosis for which she received transdermal fentanyl and hydromorphone hydrochloride for chronic pain and oxycodone hydrochloride as rescue medication. During the dose titration period, she achieved a successful FENTORA dose of 800 mcg. On day 99, the patient had serious adverse events of

severe accidental multiple-drug overdose and severe pneumonia. The investigator believed that the patient became confused because of her pneumonia; however, it was not know which of her opioids she may have taken. Both events resulted in withdrawal from the study.

9.2 Tabular Descriptions of Tools Employed in the FENTORA RiskMAP, and Surveys and Surveillance Systems

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP

Tool	Description and purpose	Rationale
Tools carried over from the ACTIQ RMP		
F1 blister	Tablets will be supplied in double-foil blisters (meet F1 requirements and have passed tests for child resistance and senior friendliness). F1 packaging is packaging that meets effectiveness specifications using Child Test procedure for special packaging (16 CFR 1700.20(a)(2)). The "F value" is the number of individual units (eg, tablets) to which access is obtained by a child under these testing conditions.	For FENTORA, access to a single 100-mcg tablet by a child could produce serious personal injury or serious illness. Under these conditions, F1 means that during such testing should a child be able to enter the package and gain access to 1 or more placebo test tablets, the package will fail for that particular child. Cephalon will distribute placebo blister packages to prescribers to help facilitate a discussion between the prescriber and patient, whereby they are demonstrating the safe administration of the tablet. This tool is designed to minimize the potential for accidental exposure to FENTORA.
Carton label	Carton labeling will be color coded by strength and contain warning information and a reminder pharmacist checklist to prompt pharmacist to counsel patient about the 2 principal risks associated with use of FENTORA. Carton label also directs patient and/or caregiver to read medication guide for important warnings. After patient receives FENTORA from pharmacist, outer carton labeling is intended to provide important warning language. The carton contains an inverted triangle symbol in multiple panels, which now is recognized by patients as a means of conveying important warning information. Each package includes a special "pharmacist box" that incorporates series of reminders to pharmacist, including pharmacist checklist. The checklist and other reminders have recently been updated for current RiskMAP to instill greater understanding of appropriate dosing paradigm for FENTORA. Recent clarifications and/or enhancements to pharmacist checklist include the following: ◆ warnings that when they dispense they should never substitute FENTORA with another fentanyl product ◆ reminders to look at prescription for FENTORA with regard to dosing and patients switching to FENTORA from another fentanyl product should not be converted on a mcg-per-mcg basis	The color coded by strength carton labeling was an effective differentiator when used with ACTIQ and hence was incorporated into the FENTORA RiskMAPs. The packaging for FENTORA provides an opportunity to "intercept" pharmacist during dispensing process with reminder pharmacy messages and an inverted triangle containing safety messages. Both were conceived with ACTIQ but enhanced when incorporated into the FENTORA RiskMAP. The symbol, in conjunction with the boxed warning, increases perceived importance to warning message to keep product out of the reach of children. It has become associated with importance of safe storage and use and disposal in packaging materials directed to patients.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Tools carried over from the ACTIQ RMP (continued)		
Carton label (continued)	The other messages of the pharmacist checklist include the following: ◆ make sure that patient is receiving predefined amount of opioid prior to receipt of FENTORA ◆ counsel and instruct patient to read medication guide ◆ remind patient to read medication guide each time he or she fills a prescription because information could have changed	
Medication guide (originally patient leaflet)	The FENTORA medication guide will emphasize the 2 principal risks associated with use of FENTORA and will reinforce appropriate patient selection and dosage and administration instructions. It includes information such as the following: ◆ warns patient of potentially serious consequences, including death, that may occur as a result of overdose when using FENTORA in an opioid-nontolerant patient ◆ warns that patient may become physically dependent on opioids and could become addicted to FENTORA ◆ warns that FENTORA is to be kept out of the reach of children and that FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine ◆ FENTORA can cause life-threatening breathing problems if taken by anyone who is not already taking other opioid pain medicines (ie, not tolerant to opioids); warning is prominently displayed as the 1st detail provided under the heading, "What is the most important information I should know about FENTORA?"	The medication guide is consumer-friendly prescribing information intended to address the most important safety information about a product to assure its safe use by a consumer. ACTIQ had originated with a patient leaflet; however, when FENTORA was being developed it was identified that a medication guide would be a stronger tool to convey this important information because it has a consistent format and content requirements across products in accordance with FDA regulations and hence has a greater likelihood of effectively communicating the messages to the patients. Recent enhancements include a description of patients who should never take FENTORA, instructions for when to stop taking FENTORA, what to do if signs or symptoms of a serious adverse event occur, and instructions regarding safeguarding of product. Additional information is provided under the heading "Who should not take FENTORA," where medication guide prominently displays that patients should never take FENTORA for treatment of short-term pain, injuries, surgery, or headaches. With this information, Cephalon can help aid patient in recognizing appropriate patient selection for FENTORA to ensure safe use.
Package insert (PI)	The package insert will contain a boxed warning about life-threatening risks associated with use of FENTORA in opioid-nontolerant patients; misuse, abuse and diversion; and accidental exposure to the medication. A boxed warning informs prescriber not to use FENTORA in opioid-nontolerant patients, to distinguish between opioid-exposed (prn) and opioid-tolerant patients, gives examples of patient populations at greater risk for being not tolerant to opioids, and specifically delineates contraindicated population indications.	The PI should always be the product's most comprehensive repository for important product information and hence it should serve also as a principal component in risk management. The PI included in this sNDA incorporates command language, directing prescribers who are the appropriate patients for FENTORA as well as who are the patients that should not be prescribed FENTORA. Prominence is given to patient selection, specifically distinguishing between opioid-exposed (prn) versus opioid-tolerant, contraindicated populations, and populations at risk for abuse and diversion.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Tools in ACTIQ RMP (continued)		
Educational introductory letters to healthcare professionals	Cephalon will develop and disseminate an educational FENTORA introductory letter reinforcing the 2 principal messages of the RiskMAP. These letters will inform HCPs of appropriate patient selection and dosing instructions for FENTORA to reduce risk of overdose and risk for abuse and diversion associated with use of FENTORA. At the time of launch, the letter will be disseminated via direct mail to 10000 identified HCP targets, all currently stocking retail pharmacies and the top 25 pain centers of excellence. Direct mail alerts, which will include a prominent display of the warning information and full product information, will be provided to inform prescribers about the approved new use of the product. These materials will also include language directing the reader to where he or she can learn about how to mitigate the risks and employ tools that Cephalon has included in their RiskMAP. NOTE: A comparable letter will be sent to drug diversion authorities emphasizing the risk of abuse and diversion. These proactive communications will educate interested parties and alert them of ways to safeguard against the potential diversion of FENTORA. This letter also includes mention of risk of abuse because patients who abuse the drug may be at increased risk for diversion.	Introductory letters and direct mail are historically part of a product's launch cycle. However, Cephalon has incorporated such introductory letters into their risk minimization programs in efforts to increase awareness both of the product's benefits but also of its' risks and how to safeguard again such risks. Such letters were employed with the initial approval of FENTORA and have allowed then for the field representatives the opportunity to provide greater information.
Risk management training for field representatives	In addition to product-specific training, field representatives will receive both home-study and live RiskMAP-specific training. The live training will be presented by Cephalon's Regulatory Affairs department. Upon completion of the training, field representatives will be tested on the training and will be required to verify their understanding of the information, including the 2 principal risks identified in the RiskMAP.	The purpose of this training is to ensure that all field representatives are consistently trained on the FENTORA RiskMAP and that the field representatives understand the FENTORA RiskMAP, the tools that are included in the RiskMAP, and how the tools can be use for each of the respective audiences. This training also provides a forum for the Cephalon internal staff to obtain feedback from the field force in efforts for ongoing improvement to the tools.
Product returns and disposal	Cephalon will accept returns for disposal of unwanted FENTORA.	This will be a tool to minimize the amount of excess product available.
Prescriber and pharmacist education (internal)	Cephalon will implement medical education directed to "geographic hot spots" that focus on preventing and/or minimizing misuse, abuse, and diversion of prescription drugs. The format of these programs will be tailored to specific need (eg, symposium, teleconferences, print materials, etc.).	Prior to the initial approval of FENTORA, Cephalon did prospective education to what were considered "geographic hot spots" at that time. The rates of abuse and diversion have been very low since the approval Cephalon will continue such programs prospectively as well as if they were to observe a signal that warranted more specificity in education.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Tools in ACTIQ RMP (continued)		
Independent Continuing Medical Education (CME)	The CME program Emerging Solutions in Pain (ESP) includes an ESP tool kit comprised of various components directed to foster comprehensive prescriber education on appropriate patient selection, identification of aberrant or drug-seeking behaviors, screening tests to employ when considering starting a patient on opioids, and the technique to monitor patients once an opioid is prescribed.	This CME initiative, the ESP program, was developed with a primary objective to help reduce abuse and diversion. CME to further education of prescribers and enhance understanding of appropriate patient selection for use with opioids and best practices for pain management will be conducted (NOTE: CME programs will be conducted in accordance with FDA and ACCME guidelines).
Reports of diversion and abuse	Cephalon will continue use of an active monitoring system (eg, RADARS®) for FENTORA. Reports from the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on FENTORA.	Reports obtained from these sources will be reviewed regularly to determine when and what intervention needs to be employed.
Web site	On the FENTORA web site, prescribers can access information at any time on safe use for FENTORA and can learn more about appropriate prescribing of opioids and patient selection. Because many patients today tend to be "active information seekers," the FENTORA web site will contain a patient-friendly entry portal allowing patients to obtain information to aid in using FENTORA in a safe manner.	The website allows for healthcare professionals and patients who are information seekers to have entry portals dedicated to the respective audiences with comprehensive information on how to appropriately use FENTORA.
Blister label	The blister label contains warning information that FENTORA should be kept of the reach of children and that it is only for patients already taking opioids; it also contains instructions for use.	When designing the FENTORA blister label, significant efforts were made to assure important safety messaging went on all facets of packaging, not just the outer carton container. The blister label is the last point just prior to patient use that we have the opportunity to provide patients with important instructions for safe use.
Pharm Alert	Educational material that reinforces the 2 principal messages of the RiskMAP will inform pharmacists of the appropriate patient selection to use FENTORA to mitigate overdose and inform them of the risk of abuse and diversion associated with use of FENTORA. These will be distributed to 40000 retail pharmacists.	It was learned from ACTIQ that pharmacy journals and other newsletters were not getting the reach and understanding. The Pharm Alert system provides greater reach in messaging to the pharmacists most likely to dispense FENTORA.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
FENTORA RiskMAP		
Prescriber education to pain centers of excellence	Cephalon will send a letter to each of the identified top 25 pain centers of excellence to offer further educational opportunities about FENTORA, including the 2 principal risks identified in the RiskMAP, ie, risk of overdose resulting from either misuse or use in opioid-nontolerant patients and the risks for abuse and diversion to FENTORA. The educational platform for these offerings will include symposia and/or teleconferences.	Cephalon has incorporated these introductory letters into their risk minimization programs in efforts to increase awareness both of the product's benefits but also of its' risks and how to safeguard again such risks.
Pharmaceutical compendia	At time of approval, Cephalon will send letter to suppliers of educational compendia and pharmacy education suppliers, such as Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons, informing them of the 2 principal risks associated with use of FENTORA and about prominent safety messages throughout the RiskMAP and providing important product information.	Pharmaceutical compendia are a significant source of where HCPs obtain their written education on a product and hence this is the rationale for sending introductory letters to these suppliers as well as any product updates.
Counseling messages (ie, directed to pharmacy software)	Because many pharmacies provide computer-generated counseling sheets along with dispensed prescriptions, Cephalon will correspond with suppliers of the information system used by pharmacies, informing them about FENTORA, the 2 principal risks associated with it, and its contraindications (eg, First Data Bank, Health Resources).	Provision of counseling messages to these suppliers will facilitate likelihood of dissemination of computer-generated counseling sheets about the safe use of FENTORA.
Counseling aids (Frequently Asked Questions [FAQ] Brochure)	An FAQ brochure was developed that describes common questions and answers about use of FENTORA. Significant modifications have been incorporated into all patient materials with regard to dosing algorithm for FENTORA. The dosing instructions have been segmented into 1) initial dose, 2) titration dose, and 3) maintenance dose to provide patient with simplest but most thorough way of ensuring proper administration of FENTORA.	Through focus groups, consultant meetings, market research, surveys, Cephalon has gathered consumer and healthcare questions about FENTORA. The FAQ, written both for the healthcare professional and one written for the patient, is intended to address the common questions and answers these audiences have in efforts to facilitate the safe use of FENTORA.
Presciber education targeted to members of professional societies	Professional societies will be contacted to offer educational opportunities to learn about FENTORA and key messages and risks described in RiskMAP, including risk for misuse, abuse, and diversion. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.	Professional societies are a major source or provider of ongoing continuing professional education and hence Cephalon believes provision of education specifically to these societies would help reinforce the safe use of FENTORA.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
FENTORA RiskMAP (continued)		
Patient kit with safety debit card	A patient kit, including patient use demonstration video, an FAQ brochure, placebo pack to help aid in patient practicing administration of tablet prior to use of actual medication, caregivers' brochures, pain diary, and safety debit card system (which is currently being piloted) that provides patient with co-pay reduction and safety message intervention component prior to patient receipt of medicine, will be disseminated to patients by prescribers and foster discussions between prescriber and patient prior to dispensing of medicine. With the safety debit card program, patients will receive additional education about safe use of FENTORA after they have received their prescription but before receiving the medication. During program, predefined sample of patients will receive patient kit containing safety debit card offering discounts on patient's co-pay. To activate card, patients must listen to important safety messages, including instructions for dosage and administration, prior to receipt of FENTORA. The safety debit card program is important because pharmacy counseling may not consistently occur; it will provide another point of intervention to ensure patients are getting necessary information before they receive the medicine.	The patient kit was designed to be a prospective intervention that contains several consumer-friendly tools that inform the patient (as well as caregiver) of the safe use of FENTORA. Cephalon recognizes that prescribers have limited time with their patients and pharmacies are limited in their counseling time, so it is believed that a patient starter kit inclusive of an innovative technique for patients to receive safety messages about FENTORA safe use prior to receipt of their medication, will be important. Cephalon will also have real-time data and metrics on the patient kits distributed.
Notify Rx messaging (pilot)	This real-time intervention will provide electronic messaging to pharmacist at point of dispensing FENTORA to ensure that pharmacist reviews important information with patient prior to dispensing FENTORA, such as safeguards patient should employ to minimize risk for diversion after taking possession of medicine; messaging in this program can also be utilized to help aid pharmacists in recognizing aberrant behaviors.	The Notify Rx messaging program (pilot) was incorporated as a result of post marketing data obtained, specifically prescribing and dispensing errors regarding conversion from ACTIQ to FENTORA. Cephalon believes this intervention will help increase pharmacist awareness and includes hard-stops such that the pharmacist is required to go through the important safety messages.
Additional tools proposed for sNDA FENTORA RiskMAP		
Healthcare education (PROTECT)	The PROTECT program, a comprehensive educational initiative, will be sponsored by Cephalon. Key opinion leaders will develop and deliver programs to medical audiences. Programs will be both FENTORA-specific and nonbranded and will focus on appropriate prescribing of opioids, appropriate patient selection regarding opioid-tolerance requirements, and proper dosing and administration requirements. These programs will be delivered by various means, including face-to-face lecture series, webinars, CD-ROMs, teleconferences, and written materials to support different manners in which professionals learn.	This program has evolved from generic healthcare education that was disseminated with ACTIQ to recognize a need for more targeted specific education. Additionally, it was learned that peer-to-peer education is the most effective educational vehicle and hence the rationale for developing a program by key opinion leaders for delivery to healthcare professional audiences.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Additional tools proposed for sNDA FENTORA RiskMAP (continued)		
RFID	Radio frequency identification (RFID) technology, which will be incorporated to further safeguard supply integrity to reduce potential diversions, will be employed in accordance with pertinent state legislation to monitor chain of custody.	This tool was identified as having great potential to the pharmaceutical industry to help reduce diversion; however, the ability to implement this tool and determine its value is currently limited by a lack of available hardware applications (ie, RFID readers) in distribution centers and pharmacies.
PEDIGREE	Electronic drug pedigree (PEDIGREE) requirements will be met to further safeguard the supply integrity to reduce potential diversions; it will be employed in accordance with pertinent state legislation to monitor chain of custody.	This tool was identified as having great potential to the pharmaceutical industry to help reduce diversion; however, the ability to implement this tool and determine its value is currently limited by a lack of available hardware applications (ie, RFID readers) in distribution centers and pharmacies.
Tamper-resistant prescription pads	Tamper-resistant prescription pads will be offered to prescribers to help them safely write prescriptions for FENTORA while mitigating risk of diversion.	With increased concern about potential for increased abuse and diversion, tamper-resistant prescription pads allow prescribers a greater confidence that once they have identified the appropriate patient for prescribing FENTORA, they have minimized a risk of fraudulent prescription writing and hence minimized risk of abuse and diversion.
Catalina Newsletter	This newsletter, which will have additional safety messages regarding FENTORA for patient, is intended to be attached to each prescription prior to it being dispensed to patient.	This newsletter was incorporated as another vehicle to provide patients with important safety information about FENTORA before they use their medicine. The newsletter is intended to compliment the medication guide. Where the medication guide is comprehensive about the safe use of FENTORA, the Catalina Newsletter is focused on specific dosing safe use messages to increase understanding.
Auxiliary Rx labels	Auxiliary labels containing reminder safety messages will be provided to pharmacists for application to cartons at time of dispensing.	Placing these auxiliary labels on carton prior to dispensing will serve as another reminder to pharmacist to ensure that patient is properly counseled.
Pharmacy checklist	A pharmacist checklist, identical to that included on the outer carton labeling, will be provided as pad, sticker, and/or stamp to aid pharmacist in counseling patient. When prescription is filled, pharmacist will counsel patients again on appropriate dosage and administration instructions accompanying patient's prescription and important safety reminders regarding maximum doses patient may take and interval of time to wait between doses; this will help reinforce prescriber's directions.	Survey data found value in use of pharmacist checklist on package; thus, by employing this systematic approach in another format, the likelihood will be increased of pharmacists providing important counseling to patients.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Additional tools proposed for sNDA FENTORA RiskMAP (continued)		
Book on opioid prescribing	Cephalon will sponsor dissemination through FSMB of "Responsible Opioid Prescribing" book to all HCPs with a DEA certificate. Cephalon field representatives may also disseminate to ensure HCPs receive this important tool. The book is authored by key opinion leaders in field of pain management and includes diagnostic tools to aid prescriber with appropriate patient selection.	Cephalon recognizes that education must be disseminated in different formats to increase likelihood of effectiveness. It is believed that distributing a book on responsible opioid prescribing, by a key opinion leader in the field of pain management, will aid prescribers who are more information seekers and prefer books to live workshops.
Resource folder	Cephalon medical personnel and the promotional review board will, on an ongoing basis, identify leave-behind literature pieces in support of risk management. At launch, the following pieces will be included: ◆"Urine Drug Testing in Pain Medicine"; Howard Heit; Journal of Pain and Symptom Mgmt; vol. 27, No.3; March 2004; pp: 260-7 ◆"Model Policy for the Use of Controlled Substances for the Treatment of Pain" Federation of State Medical Boards of the United States, Inc.; May 2004	Cephalon recognizes the historical effectiveness journal articles has had in educating healthcare professionals and wants to incorporate this venue for distributing literature in support of risk minimization and safe use of FENTORA.
RiskMAP core visual aids	This core visual detail aid incorporates patient tear-away sheet that fully describes risk of overdose possible with use of FENTORA, describes how this risk may be mitigated through appropriate patient selection (ie, must be opioid tolerant, must not be at risk of accidental exposure or misuse and abuse), describes proper dosing and administration of FENTORA, and describes proactive measures to store FENTORA in a safe and secure place to protect from theft or accidental exposure. The pharmacist will also be provided patient tear sheets.	Prescribers and pharmacists will be informed in person of the key messages and elements of the FENTORA RiskMAP, including the potentially life-threatening risk of overdose due to accidental use of FENTORA in children or adults or exposure by an individual not tolerant to opioids, the high potential for FENTORA abuse, and the risk of misuse and diversion. A patient's 1st introduction to FENTORA will be the prescriber's directions about the product, including the provision of a patient tear sheet, which will be in consumer-friendly language.
Speaker Programs	There are 2 types of Cephalon Speaker Programs (CSPs), as follows: ◆a branded CSP to provide education highlighting the risks and benefits specifically of FENTORA ◆a nonbranded CSP to educate prescribers about the risks of abuse and diversion with schedule II opioids and how to mitigate such risks in clinical practice	To accommodate different learning styles and actively engage prescribers in the learning process, CSPs will be conducted, with speakers fully trained on the FENTORA RiskMAP, who will be provided with a standard slide kit to educate other HCPs on the RiskMAP.

Abbreviations are the end of the table.

(continued)

Table 9-1: Descriptions and Rationales of Tools Employed in the FENTORA RiskMAP (Continued)

Tool	Description and purpose	Rationale
Additional tools proposed for sNDA FENTORA RiskMAP (continued)		
Speaker training	Cephalon will formally train speakers on aspects of FENTORA consistent with risk information in package insert, including key elements and messages of the RiskMAP. Speakers will be given a core slide deck containing risk and safety messages, which must be used in all speaker programs, and with approved supplemental RiskMAP slides for use at speaker's discretion. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the 2 principal risks associated with use of FENTORA. Evaluations provided will monitor whether speakers presented the required risk information	To assure speakers are consistently educated on the FENTORA RiskMAP, Cephalon provides speaker training. Additionally, this training serves to provide Cephalon with the assurance that the speakers understand the RiskMAP and the contents of the programs they are to present on the FENTORA RiskMAP.
Safety letters responding to reports of inappropriate patient selection and/or dosing	These letters will be sent out to prescribers if Cephalon learns of inappropriate prescribing through patient selection and/or dosing.	The purpose of including these letters in the RiskMAP is to assure significant efforts are always being made in increasing appropriate prescribing. Since inappropriate prescribing may occur by healthcare professional that Cephalon field representatives are not permitted to see in person, Cephalon will use letters to communicate the appropriate prescribing information.

RiskMAP=Risk Minimization Action Plan; RMP=risk management program; ACTIQ=oral transmucosal fentanyl citrate; CFR=Code of Federal Regulations; prn=as needed; HCP=healthcare professional; CME=continuing medical education; sNDA=supplemental New Drug Application; NADDI=National Association of Drug Diversion Investigators; PDR=Physician's Desk Reference; AHFS=American Hospital Formulary Service; CD-ROM=compact disc read-only memory; RFID=radio frequency identification; CP=Cephalon Speaker Program; Rx=pharmacy; ESP=Emerging Solutions in Pain; RADARS®=Researched Abuse, Diversion and Addiction-Related Surveillance System; FDA=Food and Drug Administration; ACCME=Accreditation Council for Continuing Medical Education; PROTECT=Principles of Rational Opioid Therapy: Education, Communication & Translation; FSMB=Federation of State Medical Boards; DEA=Drug Enforcement Administration.

Table 9-2: Description of Prescriber, Pharmacist, and Patient Surveys

Target audience	Assessments	Additional details
Prescriber	◆knowledge of the key risks associated with FENTORA ◆knowledge of the approved indication and contraindications associated with FENTORA ◆knowledge of definition of opioid tolerance per the package insert ◆awareness that FENTORA is not equivalent with ACTIQ on a mcg-per-mcg basis ◆behavior regarding usage of titration doses ◆delivery of patient education when prescribing FENTORA	◆administered by a 3rd-party researcher every 6 months for first 2 years of program ◆sample of prescribers includes all physicians who wrote at least 1 prescription of FENTORA in previous 6 months; list to be matched to Cephalon internal data to integrate physician prescribing information with sales call data, allowing Cephalon to analyze survey results by 2 cohorts: physicians who have been visited by Cephalon representatives in a consistent manner versus those who have not ◆Cephalon will monitor number of respondents to survey; this number is affected by number of physicians who meet survey criteria and are willing to complete survey ◆on the basis of historical data obtained with ACTIQ and postmarketing data from FENTORA, a sample of 4000 physicians will yield approximately 110 physician completers
Pharmacist	◆knowledge of the key risks associated with use of FENTORA ◆awareness that FENTORA is not equivalent with and cannot be substituted for ACTIQ on a mcg-per-mcg basis ◆awareness of indication and contraindications ◆behavior regarding dispensation of medication guide with every prescription of FENTORA ◆behavior regarding delivery of key counseling messages	◆administered by a 3rd-party researcher every 6 months for first 2 years of program ◆sample frame will be developed by using list of pharmacies that ordered FENTORA in the previous 3 months ◆it is estimated that screening of 6000 pharmacists may yield approximately 40 completed pharmacist surveys; the sample size is reassessed at the completion of each survey, and efforts to increase sample size are made as feasibly possible
Patient	◆knowledge of the key risks associated with use of FENTORA ◆knowledge of the indication (regarding opioid-tolerant patients with cancer) associated with FENTORA ◆knowledge about the directions for safe use and storage of FENTORA ◆receipt and perceived utility of medication guide and other counseling tools for FENTORA	◆patients were surveyed for years under the ACTIQ RMP, and survey data provided useful information that allowed Cephalon to ascertain which tools were more effective compared with those that warranted modification to ensure patient understanding ◆patient surveys are being administered every 6 months for first 2 years after approval of FENTORA ◆sample size was approximated by using data obtained with ACTIQ; 1200 patients will be eligible to participate in this survey, of which approximately 40% to 50% are expected to complete a survey over a 1-year period ◆Cephalon evaluates patient data with each cycle and makes efforts to increase the sample size as feasible

ACTIQ=oral transmucosal fentanyl citrate; RMP=risk management program.

Table 9-3: Description of Surveillance Systems

Surveillance system	Origin	Function and features	Additional details
RADARS "early warning system"	◆initially developed and used by Purdue Pharma to minimize abuse and diversion of OXYCONTIN®; subsequently acquired by Denver Health, a nonprofit hospital system, to continue development and progression for use by other companies ◆now an independent operation under ownership of the RMPDC, Denver Health and Hospital Authority ◆data contained in databases created during development of the system is reviewed by an organized Scientific Advisory Board	◆calculates rates of prescription opioid abuse on quarterly basis for each 3-digit zip code in the country; 2 rates are generated, one based on populations and one on number of patients who filled prescription for the drug (URDD). ◆collects and analyzes data from 4 sources, as follows: — poison control centers — key informants — law enforcement and — methadone programs ◆goals of the RADARS system include the following: — identification and quantization of sentinel events involving misuse, abuse, and diversion of prescription drugs nationwide — measure rates of misuse, abuse, and diversion of prescription drugs — provide experienced and expert analysis and interpretation of data	◆Provides a method to monitor localities for signals of abuse outbreaks ◆Using RADARS data and knowledge of distribution of FENTORA, Cephalon can decide on most appropriate course of action for problem encountered (eg, contact local law enforcement and inform them of problem, dispatch medical liaisons to contact certain physicians, or contract with local medical societies to engage in specific education and/or inform wholesalers/distributors to stop shipments to certain pharmacies) ◆After receiving signal from RADARS, Cephalon will initiate in-depth examination and identify appropriate intervention ◆All data obtained will be described and included in the FENTORA Quarterly Report
DAWN	◆DEA began DAWN in 1972 with a sample of hospital EDs and MEs to collect information on EDVs caused by drug abuse and drug-related deaths ◆NIDA took over DAWN in 1980 ◆in 1992, responsibility for DAWN passed to the SAMHSA	◆at present, about 575 EDs and 150 MEs participate ◆DAWN comprises all EDs in 21 cities and contains national panel of 87 hospitals chosen to represent coterminous US ◆DAWN data are updated regularly; data collection procedures are not consistent among hospitals and, along with personnel, regularly change within a hospital ◆underreporting of drug-abuse ED visits and unaudited data in DAWN report forms limits utility of using DAWN estimates to evaluate rates of drug abuse for risk management; however, system provides readily accessible data that can be used to detect changes or "signals" in abuse rates among a population	Not applicable

Abbreviations are the end of the table.

(continued)

Table 9-3: Description of Surveillance Systems (Continued)

Surveillance system	Origin	Function and features	Additional details
DAWN LIVE!	◆ web-based continuous data collection system; "real-time" version of DAWN ◆ allows more frequent inspection of reports than DAWN, but has less confirmation and auditing of data ◆ data can be confirmed by more reliable systems such as RADARS, DAWN, and in-house postmarketing surveillance ◆ data can be analyzed for patterns regarding age groups, visit types, and possible risk factors	As defined in the DAWN LIVE! System, "nonmedical use" of pharmaceuticals includes the following: ◆ taking more than prescribed dose of a prescription pharmaceutical or more than the recommended dose (overmedication) ◆ deliberate poisoning with a pharmaceutical by another person (malicious poisoning) ◆ taking a pharmaceutical prescribed for another individual (other) ◆ documented misuse or abuse of a prescription (other)	◆ Cephalon has received authorization to access drug-related ED visit data from DAWN LIVE! Cephalon will monitor DAWN LIVE! on quarterly basis, or more frequently (if appropriate), for all ED visits related to recent use of opioids or specific products. This can help identify emerging signals regarding trends or increased rates in FENTORA-related misuse and/or abuse. ◆ DAWN LIVE! data will be used to look at ACTIQ (fentanyl citrate lozenge) for comparative purposes. Results will be integrated with other RiskMAP-derived data to assess the need for additional educational programs or risk management strategies.
Poison Control Center Data	◆ A national, real-time surveillance database that includes all human exposures reported to participating US poison control centers since 1985	◆ Cephalon receives data compiled by AAPCC; formerly TESS) in cooperation with majority of US poison centers ◆ cumulative AAPCC database now contains approximately 41 million human poison exposure cases; database is continuously updated, with approximately 6500 new human exposure cases added daily ◆ information is usually received in 6-month intervals and includes case abstracts for all accidental exposure and/or deaths reported to AAPCC	Not applicable

RADARS=Researched Abuse, Diversion and Addiction-Related Surveillance; URRD=Unique Recipient of Dispensed Drug; DAWN=Drug Abuse Warning Network; DEA=Drug Enforcement Administration; ED=emergency department; ME=medical examiner; EDV=emergency department visit; NIDA=National Institute on Drug Abuse; SAMHSA=Substance Abuse and Mental Health Services Administration; RiskMAP=risk minimization activation plan; AAPCC=American Association of Poison Control Centers; TESS=Toxic Exposure Surveillance System; RMPDC=Rocky Mountain Poison and Drug Center; US=United States.