FEBT
(FENTANYL EFFERVESCENT BUCCAL TABLET)

2005-2006 MARKETING PLAN

DECEMBER 2005

PLAINTIFFS TRIAL EXHIBIT
P-03611_00001

Table of Contents

1 Executive Summary

NDA Submitted: Aug 31, 2005 Action Date: July 1, 2006	Earliest Launch: 3Q '06 Latest Launch: 1Q'07	Patent Expiration: 2019 (Method of Use - #6,200,604)

Market Overview (as defined by Cephalon):

Opioid Category	Value			Volume		
	2004 ($ - mil)	2004 (%)	03-04 Δ	2004 (TRx - mil)	2004 (%)	03-04 Δ
Pure SAOs	$569	10%	31%	7	5%	20%
Combi SAOs	$1,043	18%	5%	126	84%	7%
LAOs	$4,169	72%	15%	17	11%	9%
Total Opioids	$5,781	100%	15%	150	100%	7%

Source: IMS - NPA & NSP (factored using WAC)

Market Size & Growth

- Opioid market is large & continues to grow in value & volume
- Long-acting opioids (LAOs) dominate market value
- Combination short-acting opioids (SAOs) dominate market volume
- Pure SAOs experienced greatest growth in value & volume, despite being smallest in both categories
- ACTIQ ($366M, + 44% vs. '03) is only branded Pure SAO & accounts for ~62% of category's value

Market Drivers

- Increase in number of chronic pain patients continues to drive prescriptions
- Aggressive treatment of pain continues to drive market value despite introduction of generics (2 largest brands recently went generic – Oxycontin® and Duragesic®)
- Pain specialists remain most productive specialty segment while PCPs drive share

Market Threats

- MCOs continue to limit access to opioids via prior authorizations & step edits
- Fear of abuse, addiction, & diversion persists among all specialties
- Treatment guidelines (regarding BTP) are still evolving

Competitive Analysis:

Company	Products	Active Ingredient	Category	2004 TRx (000)	Δ vs. '03	Comments
Endo	Percocet	oxycodone + APAP	Combination SAO	1,199.69	- 57%	Patent expired, still promoting 2.5 mg
	Lidoderm	lidocaine	Non-opioid			Post-herpatic neuralgia local anesthetic patch, exclusivity 5/06
Janssen	Duragesic	fentanyl	LAO (Q72h)	6,048.22	+ 12%	12.5 mcg patch promoted, patent expired, exclusivity 11/06
	Ultracet	tramadol + APAP	Non-opioid			Acute pain (i.e. sprains), patent expires 8/11, no unexp exclusvity
Ortho-McNeil	Ionsys	fentanyl	PCA patch			Post-operative med, estimated launch 1Q '06
Organon/Ligand	Avinza	morphine	LAO (Q24h)	660.76	+ 211%	Patent expires 11/17, no unexpired unexclusivity
Abbott	Dilaudid	hydromorphone	Pure SAO	176.95	- 10%	Injection, oral solution & tablet, patent & exclusivity expired
	Vicoprofen	hydrocodone + ASA	Combination SAO	201.75	- 84%	Patent expired, no unexpired exclusivity
Forest	Combunox	oxycodone + ASA	Combination SAO	-	+/- 0%	Acute pain (i.e. dental pain), patent exp 2/05, exclusivity 11/07
AAI Pharma	Roxicodone	oxycodone	Pure SAO	383.38	- 27%	Patent expired, no unexpired exclusivity
Purdue	MSIR	morphine	Pure SAO	93.71	- 87%	Patent expired, no unexpired exclusivity
	OxyIR/Oxyfast	oxycodone	Pure SAO	24.55	- 88%	Patent expired, no unexpired exclusivity
	OxyContin	oxycodone	LAO (Q12h)	7,120.82	- 8%	Patent expires 10/07, no unexpired exclusivity
	Palladone	hydromorphone	LAO (Q24h)	-	+/- 0%	Withdrawm from market due to interaction with alcohol
	MS Contin	morphine	LAO (Q12h)	167.28	-56%	Patent expired, no unexpired exclusivity
Alpharma	Kadian	morphine	LAO	414.67	+ 29%	20, 50, 100 mg patent expires 3/10, no unexpired exlcusivity

Sources: *IMS Health & Orange Book.*

Major companies marketing outpatient chronic pain opioid products:

- Janssen (Duragesic 12.5 mcg) – decline in promotion of Duragesic 25-100 mcg doses due to patent expiration (LAO)
- Purdue (OxyContin) – decline in promotion due to patent expiration (LAO)
- Organon/Ligand (Avinza) – greatly increased presence of this LAO over past 2 yrs
- Forest (Combunox)
- Alpharma (Kadian)
- Endo (Percocet) – although all doses of Percocet expired, still share of voice leader along with Lidoderm & DepoDur

Recently launched Opioids:

- Combunox (Forest – Oxycodone / Ibuprofen) – claims "long lasting & rapid relief"
- Reprexain (Watson – Hydrocodone / Ibuprofen)
- DepoDur (Endo – Liposome injection Morphine Sulfate XR)

Opioids in development that will be direct competitors include
- Ionysis – fentanyl patch (Ortho-McNeil, 1Q '06)
- Generic OTFC (Barr, 3Q '06)
- Rapinyl – fentanyl wafer (Endo, '07)

Note: Cephalon is presented with a unique opportunity to establish itself as a leader in pain management due to reduced promotional efforts brought on by the introduction of generics. With new products on the horizon, it is imperative that Cephalon move forward with promotional campaigns identified in the Brand Plan, ie, Pain Franchise, BTP, OraVescent® Technology, & FEBT Campaigns

Product Description:
- FEBT is fentanyl incorporated into the OraVescent® drug delivery platform
  - When small dissolvable tablet is placed along the buccal mucosa (between the cheek and gum), an effervescent reaction produces carbon dioxide and causes a dynamic shift in pH increasing dissolution & absorption
  - Other benefits of effervescence may include a reduced thickness of oral mucous layer; opened tight junctions; and increased lipophilicity of cell membranes

Indication:
- **At launch:** BTP in patients with cancer
- **10 mths postlaunch:** BTP in non-cancer patients – sNDA submitted immediately following initial approval

Dosage: 100, 200, 400, 600, 800 mcg
- 300 & 1200 mcg under consideration to match ACTIQ dose range

Safety: similar AE profile & abuse portential to CII opioids
- FEBT will employ comprehensive Risk MAP

Efficacy:
- **At launch: same as ACTIQ – BTP in cancer patients**
  - 15 min onset & up to 60 min duration
  - Rapid onset promotional claims from 3039 data will be included in launch material (subject to DDMAC review)
    - data intended to be published prior to launch & submitted in label supplement immediately following launch
- **6 mths postlaunch:** 3039 data included in label
  - 5-10 min onset & up to 120 min duration

Advantages over ACTIQ:
- Improved rate & extent of absorption, i.e. higher & earlier systemic exposure
  - Greater absorption through oral mucosa (48% vs. 22%)
  - Greater absolute bioavailability (65% vs. 47%)
- More discreet & user friendly drug delivery
- Simplified titration scheme

Position Statement:
FEBT is the first and only fentanyl buccal tablet which utilizes an effervescent reaction to provide the most rapid onset of analgesia of any oral opioid, resulting in improved patient functioning and activities of daily living.

Key Clinical Studies:

NDA:	
99-14	efficacy: CA BTP
99-15	safety: CA BTP (open label)
1026-29	PK: 4 main studies
Timing	submitted 8/31/05 action date 7/1/06

sNDA: expand indication to non-CA	
3040	safety: all non-CA BTP (open label)
3041	efficacy: neuropathic BTP
3042	efficacy: lower back BTP
Timing	submit immediately upon NDA approval, 10 mth review

Labeling Supplement: clinical trial label Δ	
3039	efficacy (onset & duration)
Timing	submit immediately upon NDA approval, 6 mth review

sNDA: higher dose	
TBD	PK Study: 2 x 600
TBD	efficacy & safety: high dose
Timing	TBD

Key Issues		Critical Success Factors
Absence of time to convert ACTIQ loyalists (pre-generic)	→	Convert ACTIQ loyalists within 90 days (pre-launch tactics)
Limited ability to differentiate at launch w/ NDA label	→	Differentiate via available data (3039, OVF tech, ROO)
Pre-launch market conditioning resources	→	Secure, align, & optimize resources
Anticipated reimbursement barriers	→	Establish appropriate price, implement tools & initiatives
Low understanding of diagnosis & treatment of BTP	→	Utilize med-ed & BTP awareness campaign
Limited KOL, society, and MCO relationships	→	Expand KOL, society, & MCO relationships
Concern of abuse, addiction, & diversion (CII)	→	Minimize abuse, addiction, & diversion

Financial Objective:

Net Revenue (mil)	2003	2004	2005F	2006F	2007F
Pure SAO	$373	$500	$711	$757	$654
ACTIQ	$238	$337	$450	$443	$180
FEBT	$0	$0	$0	$0	$105
Pain Franchise	$238	$337	$450	$443	$285
Cephalon Mkt Share	64%	68%	63%	59%	44%

TRx (mil)	2003	2004	2005F	2006F	2007F
Pure SAO	5.8	6.9	8.2	9.7	11.5
ACTIQ	0.3	0.4	0.5	0.5	0.2
FEBT	-	-	-	-	0.1
Pain Franchise	0.3	0.4	0.5	0.5	0.3
Cephalon Mkt Share	6%	6%	6%	5%	3%

Note

- Preliminary forecast from Long Range Plan based on NET Revenue, not agreed upon by all Departments (current thinking)

Assumptions (LRP):

- Moderate ACTIQ growth until launch of FEBT
  - Launch of Sugar-Free will not impact current prescribing trend
  - ACTIQ exclusivity will end 2/07 if pediatric indication is approved, if not exclusivity will end 9/06
  - ACTIQ will experience ~50-60% net substitution within 1st 12 mths
- Forecast assumes FEBT launch 2/07 (ACTIQ ped trial completed)
  - Brand Plan assumes 9/06 launch
  - Neither Forecast nor Brand Plan assume a carcinogenicity study which could extend sNDA to '08
- Prescription growth will increase when FEBT receives expanded pain label
- Favorable response to FEBT in Market Research, even compared to ACTIQ & generic OTFC.
  - Initial source of prescriptions based on as many as 25% of patients converted from ACTIQ, coupled with strong growth trend based on new patients
- Potential competitors entering in '08 & beyond may impact growth slightly but will have a greater effect on growing the BTP market than switching patients from FEBT
  - Ionysis (1Q '06) predominantly used in hospital setting & Rapinyl ('08)

Risks (Marketing identified, not factored in LRP):

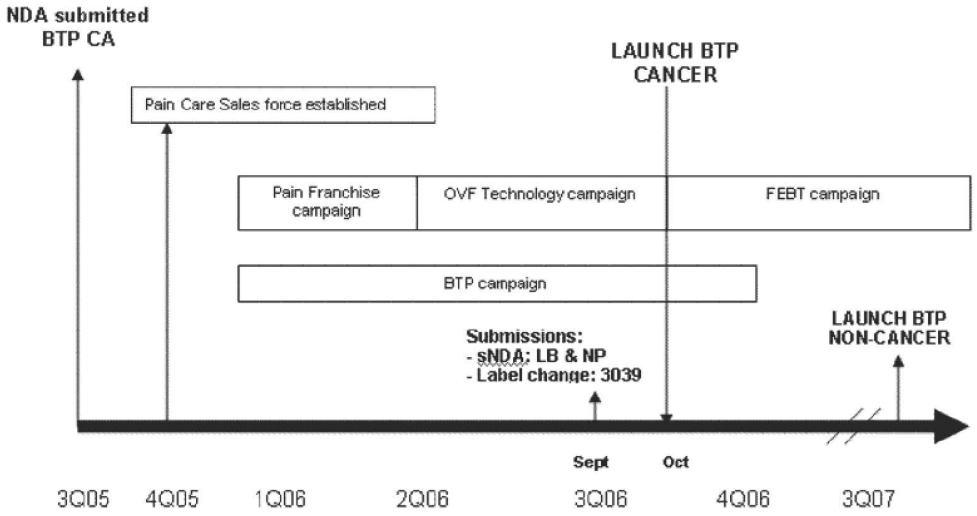
- Approval date delayed impacting time to conversion before generic
- DDMAC restriction on using 3039 data at launch
- Inability to establish ROO classification
- Appropriate FEBT pricing not established
- MCO hurdles
- Failure to negotiate optimal Risk MAP
- Unforeseen generic intrusion

Budget 2006:
The following resources are necessary to achieve the financial objectives and strategies. Interim ACTIQ activity and market conditioning campaigns will have a profound impact on the successful launch of FEBT.

Category	ACTIQ	FEBT	Both	Pain Franchise	Share
Jrnl Reprints	$150	$300	$250	$700	2%
Conventions	$473	$150	$600	$1,223	3%
A&P	$3,261	$5,000	$4,000	$12,261	35%
Coupons	$1,500	$400	$0	$1,900	5%
PR	$50	$500	$500	$1,050	3%
Field Spkr Prog	$3,000	$1,500	$0	$4,500	13%
Med Ed	$0	$4,000	$6,809	$10,809	31%
Corp Contribution	$0	$0	$200	$200	1%
RMP	$282	$250	$0	$532	2%
Market Research	$50	$1,250	$250	$1,550	4%
Consultants	$0	$275	$0	$275	1%
TOTAL	$8,766	$13,625	$12,609	$35,000	100%

Note
- Preliminary Marketing Budget based on earliest launch assumption of 3Q '06

Tactical Timeline:



Contribution Margin:

Category	2005F (mil)	2006F (mil)
Pain Franchise Net Rev	$ 450	$ 443
Marketing Expense	$ 29	$ 35
Sales Expense	$ 40	$ 23
Contribution Margin	$ 381	$ 385

Note
- Contribution includes Marketing Budget expenditures and Sales Force personnel estimate only
- Sales Expense for 2005F factored on $205K/person and included 40% of 435 reps, 45 DMs, & 8 RSDs (NAMS & NDNs not included)
- Sales Expense for 2006F factored on $205K/person and included 100% of 100 reps, 12 DMs, & 2 RSDs (NAMS & NDNs not included)

Market Overview

The Cephalon Defined US Opioid Market† totaled $5.8 billion in sales in 2004, an increase of 15% compared to the previous year. The number of prescriptions written for opioid pain medications in 2004 totaled 150 million, 7% growth vs 2003.

Chronic pain comprises 2 distinct components – persistent pain and breakthrough pain (BTP). Persistent pain is defined as a baseline pain that can be kept to a moderate intensity or less with around-the-clock opioid treatment. BTP is defined as a transitory exacerbation or flare of pain of moderate-to-severe intensity over ongoing persistent pain in patients receiving chronic opioid medication. In addition to nonopioid analgesics and adjuvant therapy, chronic pain is treated with both long- and short-acting opioids. The long-acting opioids (LAOs) are commonly used to treat persistent pain, while the short-acting opioids (SAOs) are used in addition to the LAOs for the treatment of persistent pain and BTP. Based on market research and feedback, current prescribers perceived that traditional oral SAOs provide adequate relief of a BTP episode. This clearly represents the underrecognition of typical BTP characteristics (rapid onset of pain) and the need for optimal treatment (rapid analgesia). Many physicians fail to recognize BTP as a distinct component of chronic pain, separate from the persistent pain experienced by the majority of chronic cancer and non–cancer pain sufferers. A lack of treatment guidelines specific to BTP, minimal mention of BTP in cancer and noncancer chronic pain treatment guidelines, a lack of clinical data in the literature evidencing noncancer BTP, and limited education or formal training during medical school and residency may also be contributing factors. Ultimately, this lack of understanding of the characteristics and appropriate diagnosis among opioid-prescribing physicians negatively affects their choice of therapy. Most fail to realize the need for a rapid-onset analgesic, which may be the most appropriate choice for many patients suffering from BTP. Currently a relatively small number of physicians experienced in prescribing opioids prescribe ACTIQ, the only currently available rapid onset opioid (ROO – onset of action in 15 minutes vs 30 to 60 minutes offered by traditional oral pure or combination SAOs) for their patients with BTP. While ACTIQ does address the need for rapid onset of pain relief for the treatment of BTP, its success has been limited. This is because of a combination of factors including limited physician understanding of BTP and its optimal treatment, the "lollipop" delivery system, reimbursement restrictions, and low awareness beyond a core group of opioid prescribers.

In order to create significant adoption of fentanyl effervescent buccal tablet (FEBT), Cephalon must take a 2-step approach; successfully convert ACTIQ loyalists to FEBT adopters within the first 90-day postlaunch period and expand the universe of ROO-prescribing physicians. The former step will be the priority at launch because of the loss of ACTIQ patent protection just prior to or at launch of FEBT.

Because of the absence of time to convert ACTIQ loyalists to FEBT adopters, both the market and Cephalon must be fully prepared for FEBT launch. A high level of market conditioning to drive awareness and anticipation for FEBT, establish clear differentiation, and secure favorable reimbursement at launch will be conducted prior to launch. In addition, Cephalon must be prepared to launch and execute the tactical plan immediately upon FDA approval of FEBT.

† Cephalon Defined Opioid Market includes long-acting, short-acting, and combination products containing morphine, hydrocodone, hydromorphone, oxycodone, or fentanyl.

Key Marketing Issues

Key marketing issues Cephalon must effectively address include the following:

- **Absence of Time to Convert Prescribers (generic ACTIQ available prior to FEBT launch)**
  The most significant marketing issue that Cephalon will face with FEBT is driven by the agreement with the FTC, allowing Barr Laboratories to market a generic OTFC upon FEBT final approval. The proven industry practice has been to drive product switches prior to the introduction of a generic alternative, optimally 12-18 months prior to loss of exclusivity. A successful conversion from the original product to a successor compound is largely dependent on the following variables:
    - Adequate time to establish the successor brand prior to the availability of the generic version of the precursor brand
    - Level of clear and meaningful differentiation between the precursor and the successor
    - Total level of promotional resources/share of voice applied
    - Dedicated, sophisticated, and optimally sized sales force with the successor brand in the primary selling position
    - Comprehensive managed care strategy to drive favorable reimbursement
    - Extensive patient database that will enable DTP (Direct to Patient) correspondence

  Unfortunately, Cephalon will not have the opportunity to address the most important variable in securing a successful switch – sufficient time to convert ACTIQ loyalists prior to generic availability. It is expected that Barr will launch a generic OTFC at least 30 days prior to the launch of FEBT. Retail pharmacies will update their systems for a generic OTFC alternative as soon as it becomes available. Most health plans have mandatory generic substitution policies and therefore it is predicted that the majority of ACTIQ prescriptions may be substituted. In addition, in an effort to control costs health plans may establish prior authorization and/or step edits to limit FEBT usage.

  Furthermore, prescriptions for CII products may not be refilled. Patients must see their prescribing physician on a monthly basis to receive their next CII prescriptions. Because of this, there is an opportunity to convert ACTIQ loyalists to FEBT before generic OTFC becomes firmly entrenched in the market.

  Ultimately, the lack of switch time, the immediate generic availability, and the anticipated erosion rate make the time period prior to launch and immediately following the FEBT launch (30-90 days) critical to the success of the product. To support a successful conversion of ACTIQ loyalists to FEBT adopters, it will be necessary to focus on the remaining variables that drive successful switches. Prior to launch it will be imperative to secure sufficient resources and initiate appropriate non-FEBT promotional tactics. This will help clearly differentiate FEBT and facilitate brand awareness/anticipation among ACTIQ loyalists. It will also be critical to establish a comprehensive managed markets strategy and identify the optimal size, structure, and timing for the implementation of a well-trained Pain Care sales force. Immediately postlaunch, within the first 30-90 days, it will be crucial to implement a focused Loyalists conversion strategy.

- **Limited Ability to Differentiate From ACTIQ at Launch**

  At launch the FEBT label will be based on 1 pivotal clinical efficacy trial, the 99-14 trial. The primary end point of this trial was pain relief beginning at 15 minutes postdosing.

This trial design is identical to the ACTIQ pivotal trials. Cephalon is conducting a second clinical efficacy trial in cancer patients with BTP. This trial (3039) is designed to differentiate FEBT from its competitors based on its speed of action. This study measures onset of pain relief as early as 5 minutes and time to meaningful pain relief as measured by stopwatch. This trial will not be completed in time to be included in the initial FEBT NDA. It will be submitted as a label change immediately following approval.

Note: Rapid onset claims from 3039 Study will be included in promotional launch material pending preclearance. These data are anticipated to be published prior to launch and submitted as a label supplement immediately following launch.

- **Significant Resources Required to Effectively Prepare and Launch FEBT**
  In order to effectively launch FEBT and convert ACTIQ loyalists, Cephalon will need to allocate significant budgetary and personnel resources for FEBT prelaunch and launch activities which include but are not limited to
  - Market conditioning to establish a new, emerging class of opioids (ie, ROOs)
  - Comprehensive managed care initiative
  - Medical education around BTP awareness (assessment and treatment)
  - Dedicated pain franchise personnel from supporting internal departments to ensure timely NDA approval, promotional materials availability, optimal label, and Risk MAP
  - Clinical development opportunities for Phase IIIb & IV studies

  In addition to securing sufficient resources, it will be critical to gain consensus of resource utilization among internal departments.

- **Anticipated Unfavorable Reimbursement Status**
  Third-Party Payers (TPPs) are expected to continue to drive business to generics when available and to place restrictions on premium-priced products. It is anticipated that FEBT will be premium priced. Status of TPP reimbursement of FEBT will have an impact on the success of the brand. Potential barriers utilized by TPPs to limit access may include the following; prior authorizations, usage/quantity limits, step/edit treatment requirements, and tiered co-pay structures. The development of a comprehensive managed markets plan must be completed well in advance of the launch of FEBT to minimize these potential barriers and support access for appropriate patients. The core elements of a comprehensive managed care plan include
  - Situation analysis
  - Strategies to secure favorable reimbursement
    - Document the burden of illness
    - Development of value proposition for the product
    - Determination of scenario pricing and contracting strategies
  - Tactics

- **Limited Awareness and Understanding of Appropriate Diagnosis and Treatment of Breakthrough Pain (BTP)**
  The majority of physicians believe that they are managing chronic pain adequately; however, based on market research and feedback from consultants/advisors, there appears to be a lack of understanding among many physicians about the characteristics (eg, rapid onset and relatively short duration of pain), appropriate diagnosis, assessment, and effective treatment of BTP. Many physicians fail to recognize BTP as a distinct component of chronic pain, separate from the persistent pain experienced by the majority of chronic cancer and non–cancer pain sufferers. A lack of treatment guidelines specific to BTP, minimal mention of BTP in cancer, and noncancer chronic pain treatment guidelines, a lack of clinical data in the literature evidencing noncancer BTP

and limited education or formal training during medical school and residency may also be contributing factors. Ultimately, this lack of understanding of the characteristics and appropriate diagnosis of BTP among opioid prescribing physicians negatively affects their choice of therapy. Most fail to realize the need for a rapid onset opioid, which may be the most appropriate choice for many patients suffering from BTP. It will be important to not only raise awareness of BTP (characteristics, assessment, and treatment) but also to clearly differentiate the advantages and risk profile of ROOs from SAOs.

- **Limited KOL/Professional Society/Managed Care Relationships** Cephalon is not currently viewed as a market leader in pain. Cephalon has limited relationships with KOLs, managed care decision makers, and leading pain societies compared to other market leaders. It will be important for Cephalon to be viewed as a company committed to the pain community.

- **Challenging Selling/Marketing Environment Requiring Sophistication and Expertise** The pain market is very complex and constantly evolving. Because of the potential for abuse, addiction, and diversion, CII medications are subject to stringent DEA and state regulations that are complex for pharmacies and prescribers. These include recording requirements, use of triplicate prescriptions pads in some states, special storage, non-refillable prescriptions, and sampling limitations. For example, coupon sampling programs are prohibited in the state of New York.

  Another complexity is that the undertreatment of pain continues to be a widespread problem. It has been postulated that one reason why pain is undertreated is physician fear of prescribing opioid analgesic medications (ie, opiophobia). This fear is mostly attributed to concerns of abuse, addiction, and diversion, as well as scrutiny by regulators that monitor the prescribing and dispensing of these medications. Despite mounting evidence demonstrating that effective analgesia improves quality of life, this fear persists. In general, physicians try to balance fear of opioid abuse (addiction and diversion) and regulatory scrutiny with the patient's need for medications that provide safe and effective analgesia while improving daily functioning and restoring quality of life.

  Finally, the FDA requires all newly approved schedule II opioid products to implement a comprehensive Risk Minimization Program that meets the standards set by the Guidance for Industry Development and Use of Risk Minimization Action Plans.

  All of the aforementioned factors contribute to the difficulty and complexity of selling/marketing a CII medication. In addition, Cephalon will again be marketing an opioid in a novel delivery system. As with ACTIQ, Cephalon will face challenges inherent to establishing a new delivery platform in a class dominated by oral tablet formulations. Therefore, it is imperative for Cephalon to establish the appropriate size, timing, and structure of a Pain Care Sales Force as well as pain-dedicated Medical Science Liaisons. Ideally, a Pain Care Sales Force in place by Q4 2005 would allow for the development of sufficient therapeutic expertise and adequate rapport with ACTIQ loyalists by FEBT launch (Q3 2006) to effectively execute the conversion strategy.

Commercial Vision

The commercial vision is to establish FEBT as the optimal choice for BTP.

- **Short-term (Market Conditioning):** Build market anticipation for FEBT by clearly differentiating FEBT based on its unique delivery platform and combination of patient benefits, which include rapid onset of analgesia, predictability, and ease of use.

- **Middle-term: (Year 1):** Establish FEBT as the optimal choice for BTP in cancer patients. The initial focus will be to convert ACTIQ loyalists to FEBT adopters, with the goal of switching ACTIQ patients and driving new patient starts with this existing prescribing base. This focused approach will then evolve to expand the market by adding new prescribers. In addition, appropriate nonpromotional, educational efforts will focus on creating market anticipation for the expanded BTP noncancer label.
- **Long-term (Years 2 and beyond):** Solidify FEBT as the optimal choice for the treatment of BTP.

Critical Success Factors

In order for Cephalon to continue to be successful in the BTP market post–ACTIQ patent expiration it must successfully convert ACTIQ loyalists to FEBT adopters and gain additional business from those physicians and patients who had not previously adopted ACTIQ. There are 7 critical success factors that must be addressed in order for FEBT business objectives to be achieved.

1. **Successfully convert ACTIQ loyalists to FEBT adopters within the 90-day period**

   In order for Cephalon to continue to be successful in the BTP market post–ACTIQ patent expiration it must successfully convert ACTIQ loyalists to FEBT adopters. Because Cephalon will not have time to convert ACTIQ loyalists to FEBT adopters prior to the availability of generic OTFC, the focus will be to implement alternative, proven strategies to drive conversion within the crucial 30- to 90-day period postlaunch.

   Prior to launch, appropriate market conditioning initiatives will be implemented to create the necessary awareness and anticipation for FEBT. Special care will be taken to ensure no preapproval promotion of FEBT occurs. Prelaunch initiatives will establish the OraVescent delivery technology and Cephalon as a leader in the pain market. Other initiatives will allow FEBT to be clearly differentiated from ACTIQ and other medications used to treat BTP. In addition, during the prelaunch phase, Cephalon will create and have ready for execution at launch, high-impact promotional tactics/tools that will support the rapid conversion of ACTIQ loyalists to FEBT adopters. A Pain Care Sales Force will be in place by Q4 2005 to provide the opportunity to develop relationships and rapport with key target physicians prior to launch.

   Additionally, it will be critical that FEBT is available in pharmacies as soon as possible after final approval because of the availability of generic OTFC. Currently, although aggressive, it has been determined that FEBT can be available in pharmacies 21-30 days post–final FDA approval. At present, Chemistry & Manufacturing Control (CMC), is evaluating various options in order to minimize the time from approval to product availability in pharmacies (for example, manufacturing FEBT "at risk"). This is an area Cephalon must continue to examine in order to determine the earliest point FEBT will be available for appropriate patients.

   At launch, Cephalon will begin driving conversion of ACTIQ loyalists to FEBT adopters by leveraging strong relationships and bridging from the solid market conditioning base it established prelaunch. Focused marketing and sales execution will encourage trial and usage of FEBT by ACTIQ loyalists.

2. **FEBT is clearly differentiated from ACTIQ and other BTP treatment options**

To be successful FEBT must be clearly differentiated from ACTIQ and other options for BTP treatment (eg, SAOs, and other ROOs to be launched in the future). The following product attributes will allow for FEBT to be clearly differentiated:

- Unique effervescent delivery system allowing for the rate and extent of fentanyl absorption to be accelerated
- Rapid onset of analgesia
- Ease of use, convenience
- Predictable pharmacokinetics and pharmacodynamics
- Discreet, unobtrusive administration (no handle)

3. **Sufficient resources are secured and aligned among internal departments**

Sufficient resources must be secured across all functional departments (marketing, sales, RA, SciComm, MA, pubs, managed care, etc) to effectively execute pre- & postlaunch activities. It will be necessary to have adequate investment and resources to support the following:

- Clinical and Regulatory meet their milestones
- Implementation of marketing conditioning activities
  - Establish Cephalon as a market leader in pain
  - Establish awareness for OraVescent delivery technology
  - Increase awareness of BTP (characteristics, assessment, treatment, etc)
- Determination of the optimal size and structure of the sales force
  - Fully train and prepare a Pain Care Sales Force for launch
  - It is recommended that this sales force be in place by Q4 2005
- Negotiate optimal label which clearly differentiates FEBT (inclusion of 3039 study results)
- Negotiate optimal Risk MAP
  - Focus should be to minimize risk without compromising product growth in the appropriate patient population

4. **Physicians and patients have access to FEBT**

Achieving favorable reimbursement status will be critical for the success of FEBT. As a result of an expected premium price for FEBT, it is anticipated that TPPs will seek to limit usage by placing hurdles and restrictions on prescribing. In order to obtain favorable reimbursement Cephalon must do the following:

- Demonstrate the burden of illness associated with nonoptimal treatment of BTP
- Demonstrate a value proposition of FEBT and its impact on the burden of illness of BTP
- Establish opioid category of Rapid Onset Opioids and clearly differentiate it from oral SAOs
- Provide appropriate resources to prescribers to overcome TPP barriers
- Apply appropriate resources to TPPs to gain optimal access for FEBT

Additionally, it will be critical that FEBT is available in pharmacies as soon as possible after final approval because of the availability of generic OTFC. Currently, although aggressive, it has been determined that FEBT can be available in pharmacies 21-30 days post–final FDA approval. At present, Chemistry & Manufacturing Control (CMC) is

evaluating various options in order to minimize the time from approval to product availability in pharmacies (for example, manufacturing FEBT "at risk"). This is an area Cephalon must continue to examine in order to determine the earliest point FEBT will be available for appropriate patients.

5. **Continue to develop BTP market by increasing awareness and understanding of BTP and its optimal treatment**

   Creating a high level of excitement and anticipation for FEBT will be essential to establishing FEBT in the market. The availability of generic OTFC at launch and the anticipated launch of Rapinyl® (Endo), another rapid onset fentanyl product in 2007, heightens the urgency to accelerate FEBT market penetration.

   In order to create excitement and anticipation of FEBT, Cephalon must increase physician understanding of BTP and its optimal treatment. By doing so, the market will more readily recognize the differentiating benefits of FEBT.

6. **Key Opinion Leaders support FEBT as an effective treatment option for BTP**

   KOL endorsement of FEBT will be critical to drive market anticipation for FEBT, stimulate product uptake at launch, and secure favorable reimbursement status. In addition, KOL/Pain Societies/Patient Advocacy Groups support will be crucial in efforts to secure a position for FEBT in BTP and chronic cancer and non–cancer pain treatment guidelines.

7. **Minimize risk for abuse, addiction, and diversion**

   Like other CII drugs, there will be a fear of abuse, addiction, and diversion associated with FEBT. It will be important to minimize these risks by educating physicians regarding appropriate patient selection and monitoring. In addition, patients will need to be educated about the appropriate and safe use of FEBT for BTP.

   Development and implementation of a comprehensive Risk MAP will be important to ensure appropriate patient selection and meet the FDA requirements for a Risk Minimization Program as set by the standards in the recently issued Guidance for Industry Development and Use of Risk Minimization Action Plans.

Marketing Objectives

- Achieve high level prelaunch awareness of FEBT (>90% of ACTIQ deciles 5-10)
- Strengthen relationships with core ACTIQ prescribers by increasing call frequency among ACTIQ deciles 3-10 based on PC sales force of 100 reps
  - Baseline measurement: 7.96 PDEs per decile 3-10 prescriber (6 mths, 4/05-9/05)
- Achieve 2006 ACTIQ prescription forecast (≥478K TRx in '06)
- Achieve high level awareness of ROO term (>50% of ACTIQ deciles 3-10 recognize the term by FEBT launch)
- PMEAB and KOL endorse FEBT as valuable treatment option for BTP
- Launch pain franchise and BTP awareness campaigns by 1Q06 and OV delivery technology campaign by 2Q06
- FEBT launch materials are approved and ready at launch
- Convert ACTIQ deciles 3-10 to FEBT (50% prescribed 1 time in first 3 months and 50% of trialers maintain monthly Rx over 6 months)

- Achieve high awareness of FEBT Risk MAP objectives and resources within 6 months postlaunch (>90% of deciles 3-10)
- Detail all identified FEBT stocking pharmacies within 6-month launch period

Other Department Objectives Critical to Successful Launch

- Risk MAP negotiations do not delay final NDA approval
- Sales force is in place and trained
- FEBT is stocked in all major wholesalers by launch
- Publish key clinical trials by dates established in the FEBT Publications Plan
- TPP (TBD with Health Care Systems)
    - X% are aware of FEBT by 7/06
    - X% of commercial and noncommercial plans place FEBT in a favorable reimbursement position by XXXX date
    - X% of FEBT claims are approved X months postlaunch
- Submit label supplement with 3039 data immediately upon FDA approval

Positioning

The following is the FEBT positioning statement based on the 2005 positioning market research study and the anticipated FEBT product profile:

FEBT is the first and only fentanyl buccal tablet, which utilizes an effervescent reaction to provide the most rapid onset of analgesia of any oral opioid resulting in improved patient functioning and activities of daily living.

Strategic Plan Summary

In order for Cephalon to continue to be successful in the BTP market post–ACTIQ patent expiration it must successfully convert ACTIQ loyalists to FEBT adopters within the first 90 days postlaunch and drive additional prescriptions from those physicians who had not previously adopted ACTIQ.

The 5 overarching strategies to achieve success with FEBT will be to

1. Establish Cephalon as a market leader and innovator in the pain market
2. Increase BTP awareness – definition, characteristics, prevalence, and assessment among physicians and patients
3. Create awareness around the need for an improved treatment option for BTP
4. Differentiate FEBT from ACTIQ and other BTP treatment options
5. Ensure physicians and appropriate patients have access to FEBT

The substrategies within each of the 5 overarching strategies are listed below.

1. Establish Cephalon as a market leader and innovator in the pain market
    - Initiate public awareness campaign for the Cephalon Pain Franchise
    - Demonstrate Cephalon's commitment to improving pain education and technological advances for the pain community
    - Create dedicated pain care sales and marketing infrastructure to achieve long-range plan for Pain Franchise

2. Increase BTP awareness – definition, characteristics, prevalence, and assessment among physicians and patients
    - Expand the BTP market by increasing physician and patient awareness of BTP, its diagnosis, and optimal treatment
    - Establish BTP as a clinical entity in chronic pain requiring distinct and specific treatment
    - Demonstrate the burden of illness of BTP

3. Create awareness around the need for an improved treatment options for BTP
    - Demonstrate the suboptimal nature of current therapeutic options (traditional oral SAOs)
    - Educate Healthcare Professionals (HCPs) about optimal treatment strategies for BTP
    - Establish and differentiate a new opioid class of ROOs from SAOs

4. Differentiate FEBT from ACTIQ and other BTP treatment options (ie, ACTIQ, oral SAOs, and ROOs in development)
    - Establish presence of OraVescent® delivery technology in pain market
    - Establish and differentiate a new opioid class of ROOs from SAOs
    - Demonstrate a value proposition for FEBT
    - Develop adequate and timely product education awareness via appropriate vehicles

5. Ensure appropriate physicians and patients have access to FEBT
    - FEBT available in pharmacies after final approval
    - Achieve favorable reimbursement status for FEBT
    - Establish and differentiate a new opioid class of ROOs from SAOs
    - Convert ACTIQ loyalists to FEBT within first 30- to 90-day period postlaunch
    - Increase FEBT awareness and trial by SAO loyalists
    - Expand the product label to noncancer BTP

2 Situation Analysis – BTP Market

2.1 Market Assessment

2.11 Disease Definition

Pain Classification

Pain is a prevalent medical problem that impairs the quality of life for millions. It can be short-lived, persistent for months, or debilitating for life. Pain can be classified in 3 ways: temporal aspects (acute, episodic, or chronic); cancer vs noncancer; and pathophysiology (nociceptive vs neuropathic).

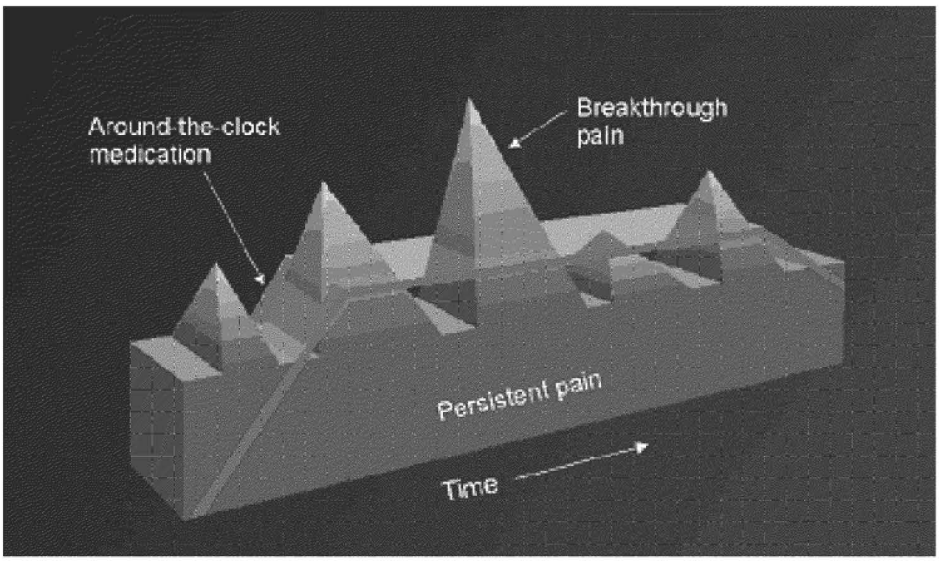
Temporal Characteristics	Acute	Pain of a relatively short duration (often defined as <3 months) that dissipates as healing occurs (eg, injury or trauma).
	Episodic	Intermittent occurrences or flares of pain, with each episode lasting for a brief period of time but recurring across an extended period of time (eg, migraine, sickle cell pain crises).
	Chronic	Pain that persists beyond the normal healing time (often defined as >3 months). Can be categorized as persistent or breakthrough pain (BTP).
Cancer vs Noncancer		Historically, practitioners viewed pain by disease state (eg, cancer vs noncancer); however, there is a shift in thinking from disease state to the pathophysiology of pain.
Pathophysiology	Nociceptive	Pain originates within normal pain pathways, appears to be proportionate with identifiable tissue damage, and has a fairly predictable response to analgesics.
	Neuropathic	Neuropathic pain is caused by damage to the nervous system, is sustained by aberrant somatosensory processing, and has a less predictable response to analgesics.

Chronic Pain

Managing chronic pain is typically more challenging than managing acute or episodic pain because of physiologic changes that occur as chronic pain develops. Moreover, chronic pain comprises 2 distinct components – persistent pain and breakthrough pain (BTP) – making it even more difficult to manage. Persistent pain is the component most associated with chronic pain, whereas BTP has a lower awareness.

Persistent Pain	Baseline pain that can be kept to a moderate intensity or less with around-the-clock opioid treatment.
Breakthrough Pain (BTP)	Transitory exacerbation or flare of pain of moderate-to-severe intensity over ongoing persistent pain in patients receiving chronic opioid medication.

Breakthrough Pain



BTP Classification

BTP can be divided into 3 sub-classifications.

Breakthrough Pain (BTP)	Incident Pain	Occurs in temporal, causal relationship with motor activity.
	Idiopathic Pain	Not associated with a known cause.
	End-of-dose Pain	Occurs before a scheduled dose of around-the-clock medication and can be ameliorated by adjusting the medication dose or dosing schedule.

BTP can strike a patient quickly and without warning (unpredictable) or it may have a more gradual onset before escalating to its maximum intensity. As a result of this phenomenon it has been difficult for physicians and patients to clearly identify, diagnose, and treat BTP separately from persistent pain. This corroborates a need for a more universal definition and understanding of BTP.

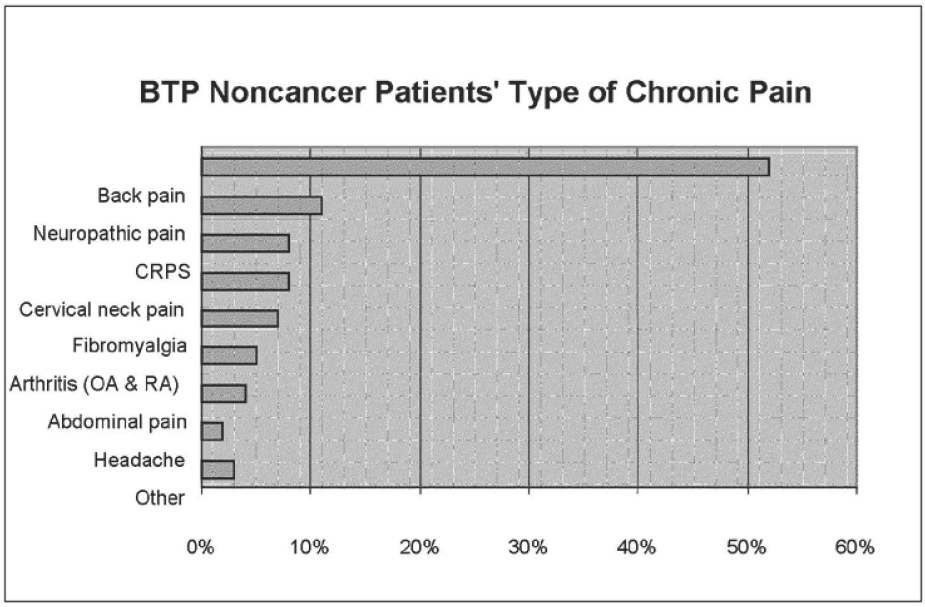
Portenoy BTP Survey

Portenoy et al conducted 2 surveys to understand BTP characteristics and prevalence in both cancer (1990) and noncancer patients (2005). The surveys revealed that there is a high prevalence of BTP in both the cancer and noncancer patient populations, with a median of 2-4 episodes/day characterized by escalation to maximum intensity in as little as 3-5 minutes and a median duration of 30-60 minutes. Cancer pain patients appear to have twice the number of episodes (median of 4) lasting ½ the duration (30 min) compared to non–cancer pain patients.

BTP Findings	BTP CA Data, '90 (n=63)	BTP Non-CA Data, '05 (n=228)
Patients experiencing BTP	64%	74%
Median # of BTP episodes/Day	4	2
Median duration of BTP episodes	30 min	60 min
Incident vs idiopathic related	55% vs 45%	92% vs 8%
Pathophysiology		
Somatic	33%	38%
Visceral	20%	4%
Neuropathic	27%	18%
Mixed	20%	40%

1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41:273-281.
2. Portenoy et al. The prevalence and characteristics of breakthrough pain in patients with chronic non-cancer pain. Abstract presented at March 2005 APS meeting.

The number of noncancer pain patients experiencing BTP is significantly higher than cancer-pain patients as a result of the respective size of patient populations. The most prevalent type of noncancer BTP is back pain, with neuropathic pain coming in a distant second.

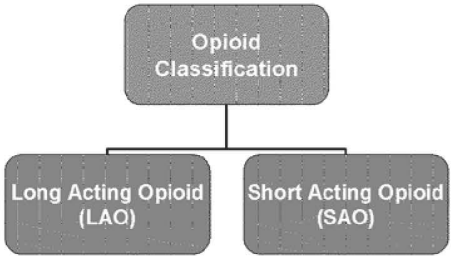


Source: Portenoy, et al. The prevalence and characteristics of breakthrough pain in patients with chronic non-cancer pain. March 2005 APS meeting poster.

Patients with BTP suffer from both physical consequences (eg, reduced functional ability and poor overall health) and psychological consequences (eg, frustration, fear, anxiety, and depression). BTP not only has a negative effect on patients' quality of life, it also increases the economic burden to both patients and the healthcare system. On average, cancer patients suffering from BTP cost the healthcare system on a per-patient basis of $12,000 per year. (Fortner, et al. 2002).

2.12 Treatment Standards and Options

Opioids are used to treat acute, episodic, and chronic pain (including BTP) associated with multiple disease states. The choice of opioid depends on the chronic or acute nature of the pain, severity, and patient tolerance or willingness to take the medication. The United States Pharmacopeia (USP) classifies opioids as either long-acting opioids (LAO) or short-acting opioids (SAO).



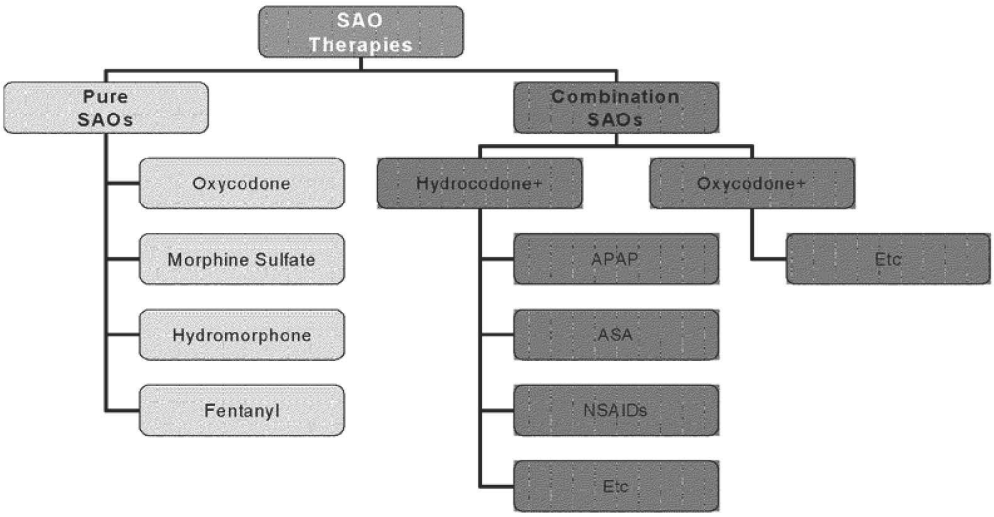
Long-Acting Opioids

LAOs are most commonly prescribed to treat the persistent pain component of chronic cancer and noncancer pain in patients who are considered opioid tolerant. LAOs are available as oral medications (MS Contin, OxyContin, Avinza, Palladone) and as a transdermal patch (Duragesic). Chronic pain is loosely defined as pain that persists for a specified time that is arbitrarily determined (eg, 3 months or 6 months) or beyond the expected period of healing. The duration of analgesia ranges from 8-72 hours, while onset of analgesia ranges from 45 minutes to 12 hours. The convenience afforded by the duration of analgesia is the key benefit of long-acting opioid products. The onset of analgesia is not a differentiating factor for LAOs.

LAOs are not considered a direct competitor in the BTP market. Various manufacturers have aggressively educated physicians to minimize the occurrence of BTP (ie, that when appropriately medicated with an LAO, patients should not experience BTP). They promote increasing the dose or the frequency of the LAO to avoid BTP flares. Although not congruent with the opinions of most key opinion leaders, many community-based physicians currently adhere to this philosophy.

Short-Acting Opioids

SAOs, which are prescribed to treat both the persistent and BTP component of chronic cancer and noncancer pain, can be further classified in terms of pure vs combination therapy. Pure SAOs include only an opioid (OxyIR, ACTIQ), while combination SAOs incorporate both an opioid and a nonopioid analgesic (ie, oxycodone and APAP, oxycodone and ASA, etc).



Pure Short-Acting Opioids

Cephalon competes in the pure SAO market. In addition to fentanyl, there are 3 pure oral SAOs on the market: oxycodone, morphine sulfate, and hydromorphone. These hydrophilic compounds are available in both branded and generic formulations. Despite the heavy reliance of the market on oral pure SAOs for the treatment of BTP, these products are less than ideal because of a lack of rapidity of analgesic effect. Onset of meaningful analgesia can take up to 30-60 minutes with these products.

Oral transmucosal fentanyl citrate, ACTIQ (OTFC), is also considered a pure SAO. Because of its unique delivery systerm, ACTIQ has a faster onset of action (15 minutes) as compared to oral hydrophilic SAOs. Current perception of ACTIQ primary benefit is rapid onset of analgesia (by both users and nonusers). For nonusers, the connection between rapid onset and the patient benefit is not fully elucidated. This will be critical for the success of FEBT.

Combination Short-Acting Opioids

Combination SAOs are the most frequently prescribed opioids (>127MM TRx in 2004). Examples of combination SAOs include Percocet, Vicodin, and Lortab. As evidenced in primary and secondary market research, opioid combination products are often prescribed for the treatment of BTP but are less than ideal for the following reasons:

- Limited dosing flexibility resulting from low opioid-dosage options (for use in mild-to-moderate pain only)
- Dose-ceiling effect because of presence of APAP, ASA, and NSAIDs causing intolerable side effects
- Onset of meaningful analgesia 30-60 minutes

Physicians use this subclass of opioids to treat acute pain, episodic, and chronic pain (including BTP) as a result of their ease of use and familiarity. These drugs do not require a complicated approval process (eg, triplicate prescriptions required in some states, CIII allow for phone-in prescriptions and refills) and have greater availability at pharmacies.

Combination SAOs (primarily hydrocodone) are frequently first-line options for both moderate and severe BTP. Pure SAOs are frequently first-line options for severe BTP; however, first-line use in moderate BTP is less prevalent (see Appendix 8: "Table 2: BTP First-line Therapy").

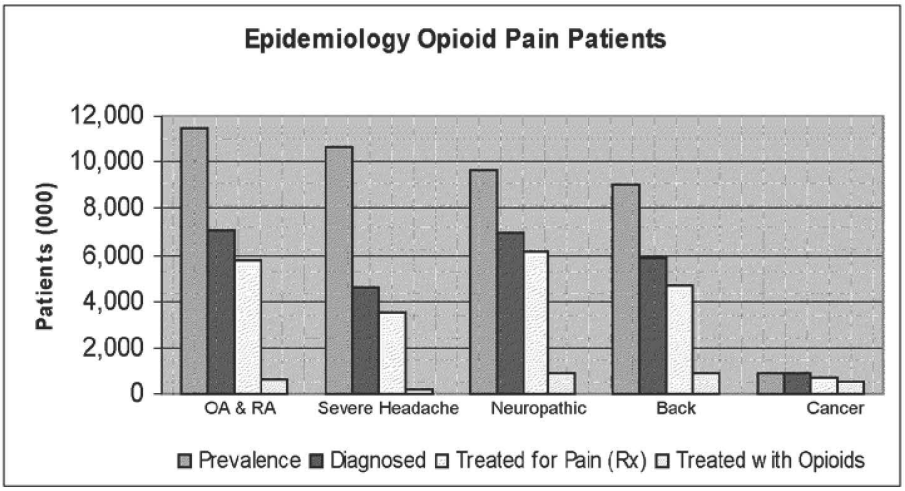
Note: *For FEBT to be successful in the opioid market, it will be critical to establish a separate and distinct class of opioids, rapid onset opioids (ROOs). This class of opioids will need to be recognized and endorsed as being specifically designed and the most appropriate to use to treat BTP. Traditional hydrophilic SAOs are generally not an appropriate treatment option for BTP because of onset of action, in contrast to lipophilic SAOs such as fentanyl.*

Abuse, Addiction, and Diversion

Unfortunately, undertreatment of chronic pain continues to be a widespread problem. It has been postulated that one reason why chronic pain is undertreated is physician fear of prescribing opioid analgesic medications (opiophobia). This fear is mostly attributed to concerns of abuse, addiction, and diversion, as well as scrutiny by regulators that monitor the prescribing and dispensing of these medications. Despite mounting evidence demonstrating that effective analgesia improves quality of life, this fear persists. In general, physicians try to balance fear of opioid abuse (addiction and diversion) and regulatory scrutiny with the patient's need for medications that provide safe and effective analgesia while improving daily functioning and restoring quality of life.

Assessment of Opioid Use by Disease State

The chart below presents derived estimates of prevalence, diagnosis rates, and treated patients by the leading disease states treated with opioids:



Source: Analysis of secondary data reports by Cephalon Market Research Department.

The prevalence of cancer-pain patients is significantly less than non–cancer pain patients; however, the percentage of cancer-pain patients diagnosed and utilizing opioids is relatively high. The vast majority of pain is therefore associated with noncancer disease states. It is diagnosed roughly 50%-75% of the time; however, it is typically treated with nonopioid analgesics. Opioid use relative to the prevalence is extremely low in the non–cancer pain population, as first-line use is typically limited to severe pain. In comparing these general pain

data with Portenoy's BTP survey identified in the previous section, it becomes clear that there is a need to study BTP therapies in areas beyond cancer – in particular in back and neuropathic patients.

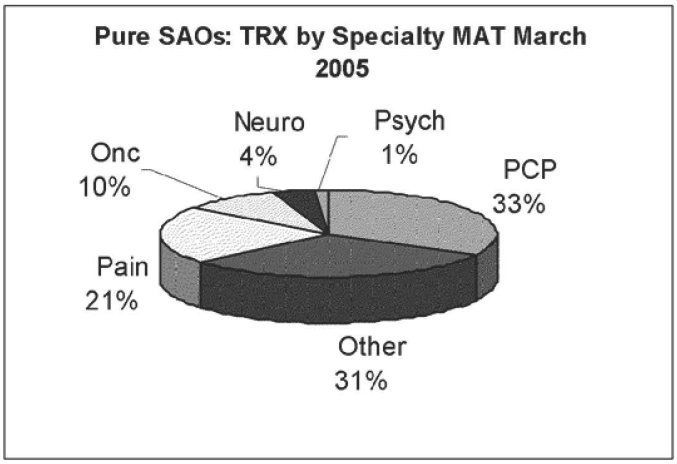
2.14 Key Stakeholders

Key stakeholders in the chronic pain market include

- Healthcare Practitioners (HCPs): Physicians, Nurses, Physician Assistants, Nurse Practitioners
- Key Opinion Leaders (KOLs)
- Pain Societies/Media/Patient Advocacy Groups
- Patients
- Regulators
  - FDA, DEA, FSMB, Law Enforcement
- Managed Care/TPPs
- Retail Pharmacists

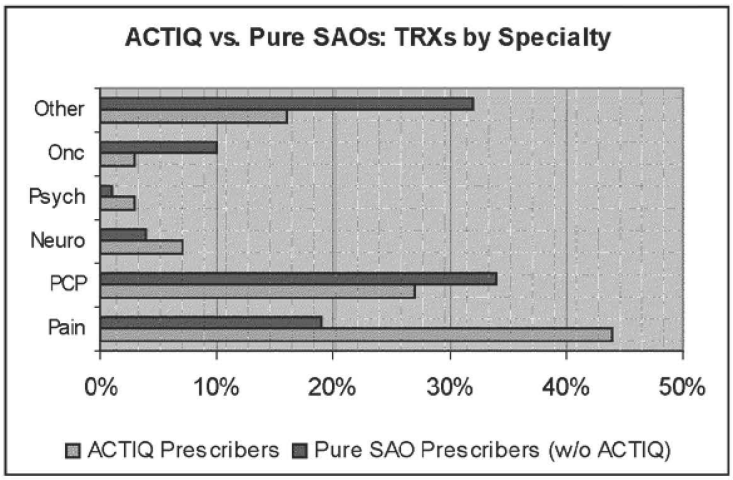
Prescribers (HCPs)

Chronic pain patients who require treatment with opioids to manage their persistent pain and BTP episodes are treated by a diverse range of specialists as well as primary care physicians. The chart below shows the percentage of pure SAO prescriptions by specialty:



Source: *IMS Health*, NPA.

Of note is the contrast of physician prescribing percentages between ACTIQ and the other pure SAOs. The chart below displays the percentage of prescriptions written by specialty segments for ACTIQ vs other pure SAOs. The majority of ACTIQ prescriptions are written by pain specialists (43%) or PCPs (27%) while the other pure SAOs are written across a greater variety of specialties. This is not unexpected because of the current ACTIQ targeting process/model, indication, and promotional practices. This difference may indicate that an expanded BTP label would provide an opportunity to introduce FEBT to other appropriate pure SAO prescribing specialties.



Source: *IMS Health*, NPA.

Productivity by Specialty Segment

Pure SAO Productivity by Specialty Segment

Specialty	Pure SAO*		ACTIQ	
	Prescriber Count 1/04-12/04	TRx / Prescriber	Prescriber Count 1/04-12/04	TRx / Prescriber
PMD	9,156	139	3,048	68
Onc	12,072	45	1,713	8
Nuero	4,010	39	848	37
PCP	102,578	22	6,051	15
A/O	104,744	13	4,000	18

Source: NDC, 2004.

* Pure SAOs includes Actiq, Dilaudid, Hydromorphone, Roxanol, MSIR, SA Morphine, Oxy IR, Oxyfast, Roxicodone, Oxycodone HCl

While a number of specialties write pure SAOs, on a per physician basis the most productive segment is Pain Medicine Doctors (139 TRx/MD in '04). All other segments are relatively the same in productivity but far less than the Pain segment (ranging from 13-45 TRx/MD in '04).

ACTIQ Productivity by Specialty Segment

The most productive physician segment for ACTIQ is also Pain (68 TRx/MD in '04). In contrast to oral pure SAOs the second most productive physician segment for ACTIQ is Neurologists (37 TRx/MD in '04). It is interesting to note there is a difference in the Oncology segment productivity for pure SAOs vs ACTIQ (45 vs 8 TRx/MD, respectively).

Key Opinion Leaders (KOLs)

KOLs are luminary HCPs and academicians who play a vital role in the success of a brand throughout its life cycle, especially with new and innovative therapies coming to market. KOLs help shape the following: clinical development plans, product positioning, brand development, life cycle management, prescribing practices, publications, medical education, managed care, etc. Studies for more than 25 years have shown that the number 1 reason a physician/HCP changes prescribing habits is peer-to-peer influence. For this reason it is important to work with these individuals to generate awareness, understanding, and appropriate use of FEBT for BTP.

Pain Societies/Media/Patient Advocacy Groups

Other groups having influence include the media and pain societies (eg, American Pain Society, American Academy of Pain Medicine, and the American Society of Addiction Medicine). Opioid treatment is associated with stigma and fear of addiction. In addition there is increasing focus on their potential for abuse and diversion. The media, pain societies, and patient advocacy groups are in a position to influence opinions on pain treatment in both positive and negative ways. For this reason it is important to work with these groups to generate awareness and understanding of appropriate use of opioids in BTP.

Patients

Another important stakeholder in the sphere of influence is the patients suffering from chronic pain. It will be important to continue to communicate to patients both pre- and postlaunch of FEBT to ensure appropriate education regarding the use of a CII medication for the treatment of BTP.

Regulators

The Cephalon Pain Franchise has been dedicated to the appropriate use of a CII medication and is a pioneer in the creation of a comprehensive Risk Management Program since the launch of ACTIQ. Cephalon is committed to minimizing the potential for abuse, addiction and diversion for ACTIQ and future opioid analgesics as they come to market. Cephalon will continue to communicate with federal and state regulators in order to achieve the most optimal Risk MAP (Risk Minimization Action Plan) and to ensure public safety.

Managed Care/Third-Party Payers

Many chronic pain patients remain marginalized by BTP because BTP is underrecognized and the economic and social value of rapid onset analgesia has not been established. A recent publication of BTP treatment guidelines indicates that the optimal treatment for BTP is a rapid ROO; unfortunately this will need ongoing validation and understanding with TPPs. Also, the chronic pain market is a highly genericized market. TPPs continually seek to control costs by driving utilization to generics or lower cost branded products. TPPs use tools such as tiered co-pays, prior authorization, step edits, and/or quantity limits to impact drug utilization. Therefore, it will be extremely important for Cephalon to continue to improve its relationship with TPPs in order to secure favorable reimbursement for a branded opioid analgesic. For this reason, a comprehensive managed markets plan will need to be executed in order to achieve favorable reimbursement status and access to FEBT for appropriate physicians and patients.

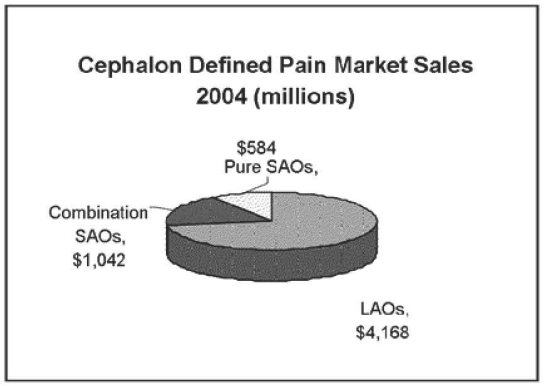
Retail Pharmacists

Another key stakeholder in the chronic pain market is retail pharmacy. Since opiophobia does not just exist in physicians and patients, it will be important for Cephalon to increase educational efforts with pharmacists around BTP awareness and its optimal treatment (rapid onset opioids). Because of the regulations and restrictions associated with CII medications it will also be important for the Cephalon Trade Relations group to execute a comprehensive pharmacy stocking plan in order to ensure FEBT is available in pharmacies 21-30 days postapproval.

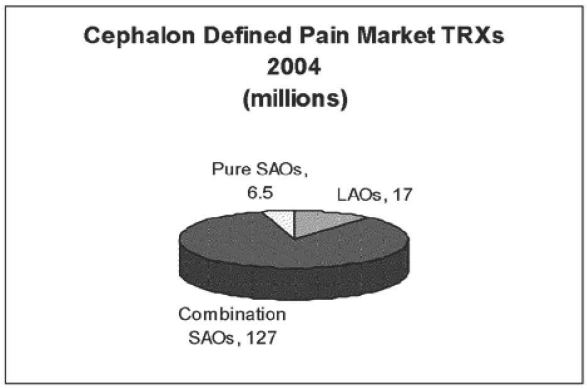
2.15 US Market Size and Overview

Cephalon Opioid Pain Market

The Cephalon-defined opioid pain market includes LAOs, pure SAOs, and combination SAOs. This market is highly genericized, with numerous generic and branded generic alternatives available in all the subclasses. Sales for this defined market totaled $5.8B in 2004, a growth of 15% compared to the previous year.



Source: *IMS Health*, SPS.



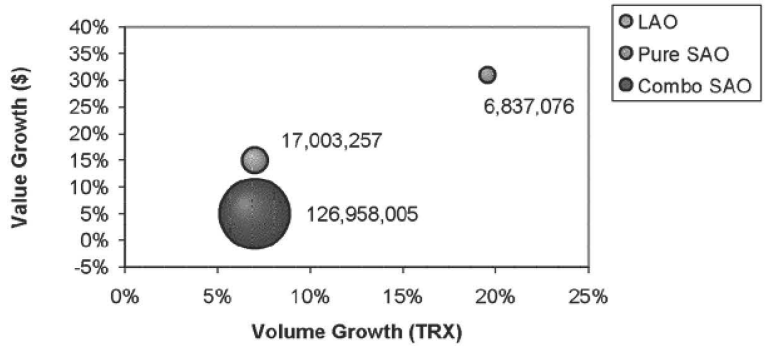
Source: *IMS Health*, NPA.

LAOs are the foundation of chronic pain management. Sales for this class totaled $4.2B in 2004, +15% vs '03. The next biggest class based in sales is the combination SAO class which had sales of $1.0B in 2004, but only +5% vs '03. The pure SAO sales total $569MM but had a growth of 36%. The majority of the pure SAO sales growth was a result of ACTIQ, which represented the majority of the sales (nearly 60%).

In contrast to sales, the dominant class in terms of TRx's is the combination SAO class with 127MM in 2004, +7% vs '03.

Overall the opioid analgesic market can be characterized as having a dominant combination SAO market segment with low value growth (+5%) and low volume growth (+7%). LAOs have a moderate prescription volume with a slightly higher value growth (+15%) but less volume growth (+7%). Pure SAO market had the highest value growth (+31%) and volume growth (+24%) but the lowest prescription volume.

2004 Opioid Market Growth*
(Size of bubble = TRx volume)



* Opioid market definition: oxycodone, morphine, hydromorphone, and fentanyl
Source: *IMS Health*, NPA = volume, *IMS Health*, NPS = value.

Cephalon BTP Market Direct Competitors – Pure SAOs

Within the pure SAO class there are 4 products: oxycodone, morphine, hydromorphone, and fentanyl. With the exception of fentanyl, all the products in the pure SAO class are available as branded or generic formulations.

Pure SAO Sales Value Analysis

In 2004, the sales for the pure SAOs were $569M, +35% vs '03. The leading product in terms of sales was ACTIQ, with $366MM (64% share), +44% vs '03. Generics totaled $135 million (24% share), +61% vs '03.

A breakdown of pure SAO value by product class is as follows:

- Fentanyl – $366MM, +44%
- Oxycodone – $105MM, +18%
- Hydromorphone – $68MM, +31%
- Morphine – $30MM, +9%

Pure Short-Acting Opioids	2003 Total Dollars	% of Total Market Dollars	2004 Total Dollars	% of Total Market Dollars	Dollar Δ 2003/2004
Total	$422,668,764	**100%**	$568,850,140	**100%**	**35%**
Oxycodone products	$89,169,264	21%	$104,919,401	18%	18%
Oxycodone HCl (8 generics)	$32,030,412	8%	$61,188,538	11%	91%
ROXICODONE	$43,611,677	10%	$36,943,592	6%	-15%
OXYDOSE	$4,578,418	1%	$6,605,710	1%	44%
OXYIR	$4,411,081	1%	$161,852	0%	-96%
OXYFAST	$4,537,776	1%	$19,709	0%	-100%
Morphine products	$27,764,597	7%	$30,369,678	5%	9%
Morphine Sulf (9 generics)	$19,965,797	5%	$26,132,392	5%	31%
Roxanol	$6,112,223	1%	$4,204,910	1%	-31%
MSIR	$1,686,577	0%	$32,376	0%	-98%
Hydromorphone products	$51,734,803	12%	$67,561,061	12%	31%
Hydromorphone HCl (15 generics)	$31,972,020	8%	$47,851,164	8%	50%
Dilaudid	$19,762,783	5%	$19,709,897	3%	0%
Fentanyl product	$254,000,000	60%	$366,000,000	64%	44%
ACTIQ	$256,096,050	60%	$366,000,000	64%	44%

Green = compound class Blue = generic Yellow = branded
Source: *IMS Health*, NSP. (based on WAC price)

Prescription Volume Analysis

In 2004, approximately 6.8 million prescriptions were written for pure SAOs, +20% vs '03. The majority of pure SAO prescriptions written in 2004 were for generics (82%). Approximately 12% of the total prescriptions were for branded products. ACTIQ captured 6% of the total prescriptions (half of all branded products).

The class prescription growth is attributable primarily to generics. The only branded products to demonstrate growth were ACTIQ (34%) and Oxydose (51%).

Pure Short-Acting Opioids	2003	% of Total Market	2004	% of Total Market	TRX Δ 2003/2004
Total	**5,718,677**		**6,837,076**		**20%**
Oxycodone products:	2,896,666		3,444,989		19%
Oxycodone HCl (8 generics)	2,090,711	37%	2,929,647	43%	40%
OXYIR	166,766	3%	18,362	0%	-89%
OXYFAST	42,976	1%	6,183	0%	-86%
ROXICODONE	527,852	9%	387,378	6%	-27%
OXYDOSE	68,361	1%	103,419	2%	51%
Morphine products:	1,526,176		1,770,311		16%
Morphine Sulf (9 generics)	1,240,055	22%	1,640,588	24%	32%
MSIR	93,707	2%	11,720	0%	-87%
Roxanol	192,414	3%	118,003	2%	-39%
Hydromorphone products:	969,638		1,185,717		22%
Hydromorphone HCl (15 generics)	773,183	14%	1,008,764	15%	30%
Dilaudid	196,455	3%	176,953	3%	-10%
Fentanyl product:					
ACTIQ	326,197	6%	436,059	6%	34%

Green = compound class Blue = generic Yellow = branded
Source: *IMS Health*, NPA.

2.16 Reimbursement/Managed Markets

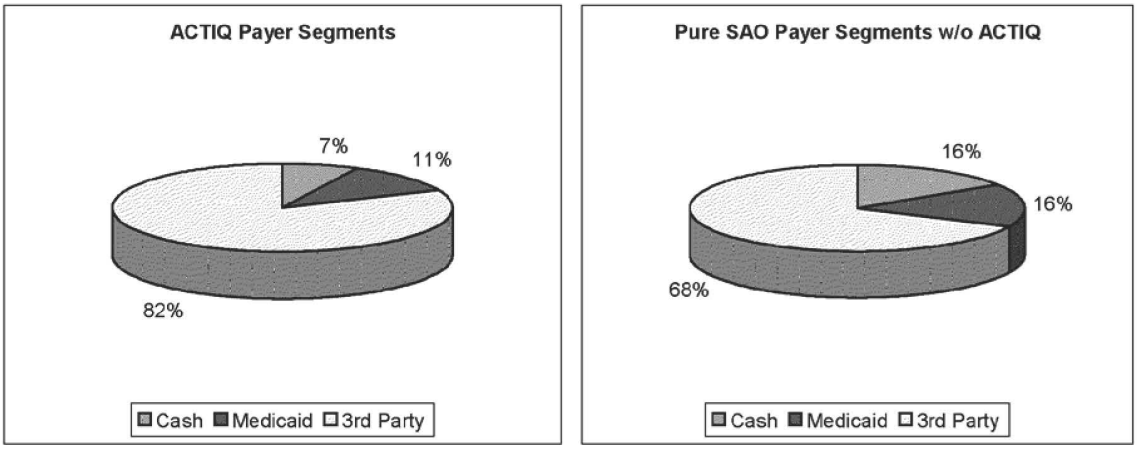
For a background on reimbursement/managed markets please refer to Appendix 1.

ACTIQ Experience in Managed Markets

ACTIQ is the best analog for analysis of the reimbursement situation FEBT is likely to face at launch. ACTIQ unit sales can be broken into 3 payers or segments:

1. Patients who pay cash for their prescription
2. Government (Medicaid)
3. Third party (which includes anyone other than the patient or government paying for a script. This would include managed care, insurers, worker's compensation, and employers).

The following charts show the contrast of payer segments for ACTIQ vs pure SAOs:



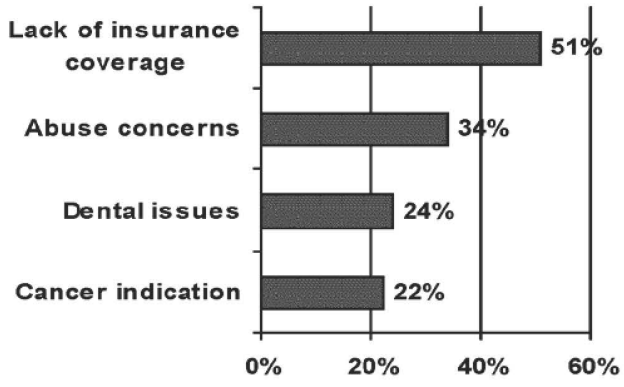
Source: 12/04 NDC SMART Plan

The premium price of ACTIQ compared to the other pure SAOs (all available in generic form) impacts the payer split percentage. The majority of ACTIQ units are paid for by TPPs (82%), while only 68% of the pure SAOs units are paid for byTPPs. A greater percentage of the pure SAOs units vs. ACTIQ are paid for by Medicaid, 16% and 11%, respectively. And particularly because of the price difference, a greater percentage of the pure SAOs are paid for with cash (16%), compared to ACTIQ (7%).

Reimbursement

BARRIERS TO ACTIQ USAGE

- **Physicians report that the biggest factor limiting usage is Payers that are using the cancer indication to limit insurance coverage of off-label usage.**



Source: Decision Development Inc, ACTIQ Pain Specialist Use Study, July '05

Reimbursement was noted as the leading barrier to prescribing ACTIQ in all recent primary research studies (ie, Pain Specialist Use Study, 7/05; Pain Market Dynamic Study, 2/05; IMS Chart Study Audit, 12/04; and Egg Study, 9/04). According to the IMS Chart Study Audit, 67% of the physicians reported having experienced insurance coverage issues with ACTIQ. With managed care organizations (MCOs) increasing restrictions on reimbursement (tiered co-pay, prior authorization, step edits, etc), FEBT will incur similar issues. These complexities have an unquantifiable negative impact on prescribing behavior as physicians become more selective in their use of ACTIQ or opt for alternatives with minimal resistance.

According to the recent Pain Specialist Use Study, all physicians (100%) mentioned ACTIQ as one of the most difficult products in which to obtain reimbursement. In fact, ACTIQ was mentioned twice as often as any other drug (among both LAOs & SAOs). Despite these hurdles, those who have persisted were able to obtain approval (94% in '04, according to the NDC Claims Database).

Fourth quarter 2004 claims data reveal the leading reasons for initial rejection related to reimbursement requirements, including lack of prior authorization (43%), which is on the rise; plan limit exceeded (13%); product not covered (11%); and DUR reject error/step edit (5%).

According to the Cephalon NAM Formulary Grid the "plan limit exceeded" is primarily associated with exceeding the "number of units covered by month." The most common limit is 4 units per day (120 units per month). A lesser number of plans cover 6 units per month (180 units). A few plans place extreme limits on quantity per month such as 6 units per 7-day period or 24 units per month.

ACTIQ Claim Rejection Reasons

ACTIQ Claim Rejection Reason	1Q03	2Q03	3Q03	4Q03	1Q04	2Q04	3Q04	4Q04
PRIOR AUTHORIZATION REQUIRED	25%	27%	28%	33%	35%	38%	40%	43%
PLAN LIMITATIONS EXCEEDED	19%	17%	15%	15%	12%	13%	13%	13%
PRODUCT/SERVICE NOT COVERED	11%	11%	9%	8%	7%	6%	9%	7%
DUR REJECT ERROR (Step edit)	4%	3%	5%	6%	6%	6%	5%	5%

Source: December NDC Dynamic Claims Analyze: commercial patients only – no Medicaid or cash patients included.

Medicaid

State Medicaid programs continue to be subjected to state budgetary pressures and therefore are increasingly moving toward preferred drug lists, quantity limits, prior authorization, appeal processes for denials, coverage for only FDA-approved indications, and supplemental rebate programs. ACTIQ serves as the best analog for FEBT. ACTIQ has been put under prior authorization in a number of states over the course of the last year and we expect this trend will continue. Currently, 27 states have ACTIQ under a prior authorization. According to the claims data, most are eventually approved; however, it is unclear what impact this burdensome process has on future physician-prescribing behavior. As many as 10 states have limited ACTIQ coverage to its indication (BTP in cancer patients) along with quantity limit restrictions. Of the 22 states that continue to allow unimpeded access, nearly half are the less populated states, so ACTIQ usage probably has little impact on their budget.

Medicare

Medicare benefit is administered and funded in 4 parts. Parts A and B only cover in-office pharmaceutical use, where Part C typically provides a generic formulary. Part D, which goes into effect January 2006, includes a new PBM administered outpatient drug benefit option which is not restricted to generics (see Managed Care Appendix 1 for background). The logistics of Part D continue to evolve. Plans will have flexibility (subject to certain constraints) to establish varying features of the formulary:

- Levels of cost-sharing requirements and coverage limits other than "standard" coverage
- Lists of drugs to include on their formulary, and on which tier
- Cost management tools, ie, PA, step therapy, tier levels

Under Part D, FEBT will have difficulty gaining formulary coverage because of the following reasons:

- Anticipated premium pricing
- Limited indication at launch
- Formularies set using USP definitions

Another concern regarding Part D is the potential for a gap in coverage for many seniors. Once a senior reaches $2,250 in total drug costs (the combination of what Medicare and the senior have paid), Medicare stops covering drug costs until the senior spends another $2,850 on medication. After this level of expenditure occurs the senior is eligible for catastrophic coverage. This gap in coverage is commonly referred to as the "donut hole." Utilization of premium priced products by Medicare Part D beneficiaries is expected to be limited due to this "donut hole" in coverage. Cephalon will continue to monitor program developments and adjust strategies accordingly.

Managed Markets Summary

Third-Party Payers (TPPs) are arguably the most important stakeholder for FEBT. Unless some reasonable level of reimbursement for FEBT is available, doctors and patients will be discouraged from using the product. The continuing trend of TPPs to drive utilization toward generics and less expensive brand alternatives will be a major challenge for Cephalon when it brings FEBT to market. This challenge will be magnified by the fact that BTP and its appropriate treatment are not well understood by the payers. It will be essential for Cephalon to educate the payers on the burden of illness associated with nonoptimally treated BTP, differentiate ROOs from oral SAOs, and to demonstrate a strong value proposition for FEBT. Because these stakeholders are of such high importance a separate Managed Markets Plan has been created to comprehensively address the issues, strategies, and tactics that have been created. See Appendix 2, Managed Markets Plan.

2.17 Product Conversion Analogs

A leading strategy employed by pharmaceutical companies to manage the loss of product patent protection is to launch a successor brand. An extensive external assessment of companies that have switched their users from one drug that was losing patent life in the near term ("the precursor") to another similar drug ("the successor") was completed (see Appendix 8: Table 1: Product Conversion Analogs Analysis, for details). This analysis revealed that successful conversion from a precursor to a successor brand includes the following variables:

- Adequate time to establish the successor brand prior to the availability of the generic version of the precursor brand
- Level of clear and meaningful differentiation between the precursor and the successor
- Total level of promotional resources/share of voice applied
- Dedicated, sophisticated, and optimally sized sales force with the successor brand in the primary selling position
- Comprehensive managed care strategy to drive favorable reimbursement
- Extensive patient database that will enable Direct to Patient (DTP) correspondence

While the analog selection criteria included non–life threatening indications and targeting towards a primary care audience, the learnings are still applicable to the FEBT situation.

Summary Learnings

Conversion Attributes	Successful	Unsuccessful
Time	Time to establish new brand before generic launch >= 12 mths	Time to establish new brand before generic launch <6 mths
Differentiation	Differentiating feature that resonated with HCPs	Differentiating feature only applicable to small % of patient population
Sales Force	Large sales force with product in primary position - Median size - 2000 reps with 93% in primary position	Only first priority for small % of sales force - Between 300-600 reps promoting as first priority
Budget	Significant promotional budget - 10%-30% of precursor product sales (the year before successor launch)	Not enough promotional dollars to support switch - 3%-5% of precursor product sales (the year prior to successor launch)
Managed Care	Before generics came to market, preferred access to important managed care plans was secured	Did not gain preferred access to managed care formularies
Pricing	Greater conversion for successor brands launched with discounted price to precursor	
Patient Outreach	Extensive patient database that enabled DTP correspondence	

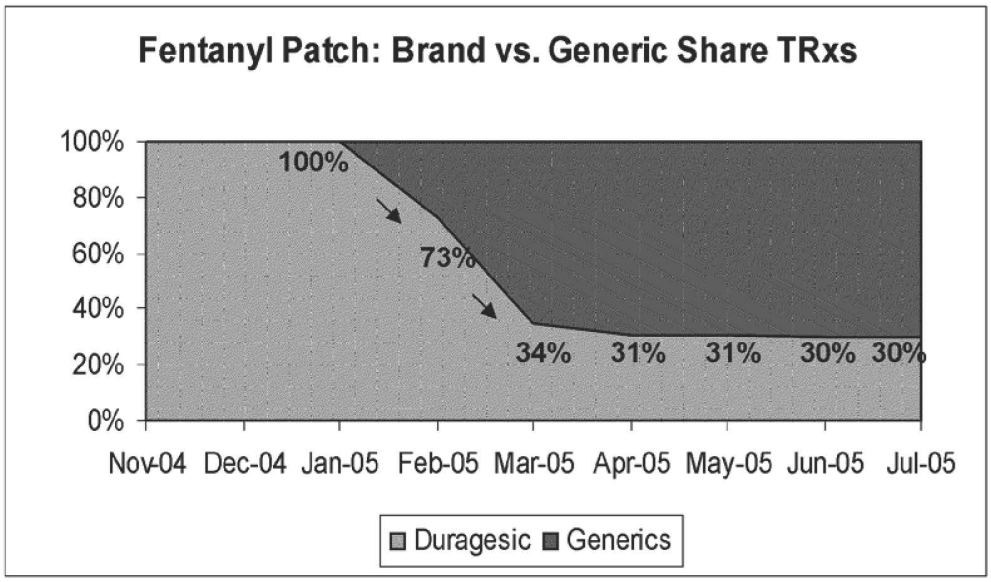
For more details on the conversion analysis, please see Appendix 11.

2.18 Generic Erosion

The rate and extent of generic erosion of a branded product's business has steadily increased over time. Generic companies are more sophisticated and payers are more effective in their efforts to influence the way prescriptions are written and filled. Unless a branded product has unique qualities/characteristics that are clinically differentiated, it will be susceptible to significant generic erosion. In general, the trend has been for branded products to lose 30% in the first month, 50%-60% by 6 months, and 80%-90% within a year, regardless of the number of

generic entrants. The most well-known example is Prozac, which lost 73% of its share within the first 2 weeks and retained only 16% at 12 months post–generic introduction. At 12 months the generics were only 15% the price of Prozac.

Duragesic may serve as the best analog for what may be expected for the erosion of ACTIQ. As discussed previously, the conversion of ACTIQ prescriptions to generic OTFC prescriptions may make it more difficult to switch patients and trial them on FEBT. In January 2005, Duragesic started to face generic erosion. In the first full month of generic competition (February), Duragesic share of the LAO fentanyl molecule was 73% and in the second month the branded product had only a 35% share of the molecule.



Source: *IMS Health*, NPA.

Two companies are marketing a generic transdermal fentanyl, Novartis and Mylan. The generics' AWP pricing is a 6.2% discount to Duragesic according to the March 2005 *Redbook*.

Trandermal fentanyl	Duragesic	Generic Avg	Discount AWP
25 mcg, 5s	$ 76.98	$ 72.14	6.2%
50 mcg, 5s	$ 140.71	$ 131.86	6.2%
75 mcg, 5s	$ 214.64	$ 201.14	6.2%
100 mcg, 5s	$ 284.87	$ 267.94	6.2%

Source: March 2005 *Redbook*.

2.19 Market Drivers

Key opioid market drivers are as follows:

- Increase in number of chronic pain patients continues to drive prescription volume (151MM TRx's, +7% vs '03)
- Market value continues to grow ($5.8B, +15%) despite introduction of generics (2 largest brands went generic, ie, Oxycontin® and Duragesic®)

- Promotion continues to decline because of branded product patent expirations
- Price erosion is anticipated to accelerate as additional generics enter the market

- MCOs continue to limit access to opioids via prior authorizations and step-edits
- Pain specialists drive opioid prescriptions
  - Fear of abuse, addiction, and diversion persists among prescribing community
- Chronic pain treatment guidelines regarding BTP continue to evolve

2.2 Competitor Assessment

2.21 Long-Acting Opioids (LAOs)

LAOs are most commonly prescribed to treat the persistent pain component of chronic cancer and noncancer pain in patients who are considered opioid tolerant. LAOs are not considered a direct competitor in the BTP market. However, LAOs have been promoted to be used to reduce/prevent the occurrence of BTP by increasing the dosage amount or frequency of the dose. Although not congruent with the opinions of most key opinion leaders, many community-based physicians currently adhere to this philosophy.

In 2004, the leading LAO in terms of TRx's was OxyContin (42% of total LAO TRx's). However, in 2004 OxyContin TRx's decreased by 8% compared to 2003. This is most likely because the 80-mg dosage strength (highest dollar volume strength) is currently available in generic form. In June 2005, Purdue Pharma LP lost an appellate court decision to Endo Pharmaceuticals on the patent protection of the 10-, 20-, and 40-mg strengths, which will expose OxyContin to an accelerated erosion rate because of the generic availability of these dosage strengths.

The number 2 product in terms of TRx's is Duragesic. Duragesic achieved a 12% increase in TRx's for 2004 (6.0MM Trx) vs 2003 (5.5MM TRx).

	TRx 2003	TRx 2004	Share of Total Class 2004	TRx Δ 2003/2004
Selected Market: LAOs	15,859,781	17,003,257		7%
Oxycodone products	7,722,662	7,440,181		-4%
OXYCONTIN	7,722,662	7,120,820	42%	-8%
OXYCODONE HCl ER	0	319,361	2%	NA
Morphine products	1,052,850	1,314,343		25%
GENERIC LA MORPHINE (3 products)	1,664,866	2,200,517	13%	32%
KADIAN A.L 96/08	321,893	414,672	2%	29%
MS-CONTIN	384,374	167,279	1%	-56%
AVINZA	212,606	660,756	4%	211%
ORAMORPH SR	133,977	71,636	0%	-47%
Fentanyl product	5,419,403	6,048,216		12%
DURAGESIC	5,419,403	6,048,216	36%	12%
Hydromorphone product	0	0		
PALLADONE (launched 1/2005)	0	0	0%	NA

Green = compound class Blue = generic Yellow = branded
Source: *IMS Health*, December 2004.

2.22 Combination SAOs

Combination SAOs are the most frequently prescribed opioids (127MM TRx's in 2004) as they are typically first-line therapy for moderate pain (vs severe pain). Examples of combination SAOs include Percocet, Vicodin, and Lortab. As evidenced in primary and secondary market research, opioid combination products are often prescribed for the treatment of BTP but are less than ideal for the following reasons:

- Limited dosing flexibility because of low opioid dosage options (for use in mild-to-moderate pain only)
- Dose ceiling effect because of presence of APAP, ASA, and NSAIDs causing intolerable side effects
- Onset of meaningful analgesia 30-60 minutes

Physicians use this subclass of opioids to treat BTP, acute pain, chronic pain, and episodic pain as a result of their ease of use and familiarity. These drugs do not require a complicated approval process (eg, triplicate prescriptions required in some states, CIII allow for phone-in prescriptions and refills) and have greater availability at pharmacies.

In 2004 the leading combination SAO in terms of total prescriptions was generic hydrocodone + APAP (77% of total combination SAO TRx's). The next most commonly dispensed combination SAO was generic oxycodone + APAP with a 10% share of total class prescriptions. The branded combination SAOs accounted for only 10% of the dispensed prescriptions. The leading branded product was Endocet, with a 5% share of the class total prescriptions.

	TRX's 2003	TRX's 2004	Share of Tot Class	TRX Δ 2003/04
Select Market: Combination SAO	**118,794,132**	**126,958,005**		**7%**
Hydrocodone + APAP products:	**94,445,767**	**100,606,442**		**7%**
Hydocodone + APAP generics	91,130,228	97,918,530	77%	7%
Vicodin	1,766,306	1,399,690	1%	-21%
Lorcet/Lortab	1,549,233	1,288,222	1%	-17%
Hydrocodone + ASA products:	**519**	**21**		**-96%**
DAMASON-P	519	21	0%	-96%
Hydrocodone + ibuprofen products	2,545,713	2,419,386		-5%
Hydrocodone + ibuprofen generics	1,313,001	2,217,641	2%	69%
VICOPROFEN	1,232,712	201,745	0%	-84%
Oxycodone + APAP products:	**21,402,587**	**23,591,375**		**10%**
Oxycodone + APAP generics	10,003,973	13,181,863	10%	32%
ENDOCET	5,336,929	6,708,519	5%	26%
PERCOCET	2,793,156	1,199,819	1%	-57%
ROXICET	3,182,055	2,439,952	2%	-23%
TYLOX	86,474	61,222	0%	-29%
Oxycodone + ASA products:	**399,546**	**340,781**		**-15%**
Oxycodone + ASA generics	56,740	93,244	0%	64%
ENDODAN	270,053	200,173	0%	-26%
PERCODAN	72,183	47,117	0%	-35%
ROXIPRIN	570	247	0%	-57%

Green = compound class Blue = generic Yellow = branded
Source: *IMS Health*, December 2004.

2.23 Pure Short-Acting Opioids

2.231 ACTIQ®

In 2004, ACTIQ sales totaled $365.9 million. The patent for ACTIQ is expected to expire on September 5, 2006, unless it receives a pediatric exclusivity 5-month extension to February 3, 2007 (1 month removed because of FTC consent decree). At this time at least 1 generic version of OTFC (Barr) is expected upon patent expiration.

A sugar-free formulation of ACTIQ is expected to launch Q1 2006.

Key product messages:

- ***Efficacy:*** Within 15 minutes of starting medication, patients using ACTIQ rated their pain relief at 67% compared to 3% with their regular rescue medication
- ***Safety:*** No pharmacologically active metabolites
- ***Side Effects:*** The most common side effects observed were somnolence, nausea, vomiting, and dizziness
- ***Dosing and Titration:*** To achieve maximum relief, patients should finish the ACTIQ unit completely in 15 minutes
- ***Convenience/Ease of Use:*** Patients can use ACTIQ anywhere without water as soon as they begin to feel breakthrough cancer pain
- ***Delivery System:*** The unique OT delivery system, allows fentanyl to rapidly dissolve into the highly permeable and well-vascularized oral mucosa
- ***MOA of Fentanyl:*** High lipophilicity of oral transmucosal fentanyl allows for rapid absorption across the oral mucosa into the blood and distribution into the CNS – a process with a 3- to 5-minute half-life

Vulnerable Aspects:

- Label indication limited to BTP in cancer patients
- Delivery system: The delivery system is perceived as indiscreet – because of the "stick" or "lollipop" design there is a high level of concern regarding its attractiveness to children; also bioavailability is dependent on user consumption technique
- Initial dose titration scheme – complicated scheme to titrate to effective dose
- Loss of patent exclusivity/competition from generics – September 2006
- Cost – expensive compared to alternative products
- Reimbursement status – because of cost and fear of abuse and diversion, TPPs place hurdles to prescribing and reimbursement

2.232 Pure SAO: Oxycodone-Based Products

Oxycodone Products	Manufacturer
Oxycodone HCl (8 generics)	Various
OXYIR	Purdue
OXYFAST	Purdue
ROXICODONE	AAI Pharma
OXYDOSE	KV Pharmaceuticals

Indication: For moderate-to-severe pain (none indicated for BTP)
Formulations: Oral solution and tablets

Dosing: Every 6 hours as needed
Onset of action: 30-60 minutes

Commercial aspects:

- Molecule: Branded generics and generics
- Only OXIR has had any audited promotional effort (Purdue)

2.233 Pure Morphine-Based Products

Morphine products	Manufacturer
Morphine Sulf (9 generics)	Various
MSIR	Purdue
Roxanol	AAI Pharma

Green = compound class Blue = generic Yellow = branded

Indication: For moderate-to-severe pain (none indicated for BTP)
Formulation: Oral solution and tablets
Dosing: Every 6 hours as needed
Onset of action: 30-60 minutes

Commercial aspects:

- Branded generics and generics
- Active metabolites M-6G and M-3G increase side effect profile

2.234 Pure Hydromorphone-Based Products

Hydromorphone products	Manufacturer
Hydromorphone HCl (15 generics)	Various
Dilaudid	Abbott

Green = compound class Blue = generic Yellow = branded

Indication: For moderate-to-severe pain (none indicated for BTP)
Formulation: Oral tablets
Dosing: The usual oral dose is 2 mg every 4 to 6 hours as necessary. More severe pain may require 4 mg or more every 4 to 6 hours.
Onset of action: 30-60 minutes

Commercial aspects:

- Branded generics and generics
- Commonly used in severe pain patients (ie, sickle cell crisis)

2.24 Pricing Analysis

The cost per dose for a pure SAO ranges from $0.21 to $1.33. The notable exception in this class is ACTIQ – on a per-dose basis ACTIQ is the most expensive SAO (range $7.37 to $21.23 per unit).

ACTIQ® Cephalon *(not inclusive of 2005 price increase)*	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	30 30 30 30 30 30	$221 $280 $343 $406 $529 $652	$7.37 $9.33 $11.43 $13.53 $17.63 $21.73
OxyIR Purdue	5 mg	100	$31.45	$0.31
OxyFast Purdue	20 mg/mL	30	$37.00	$1.23
Oxycodone tablets Mallinkrodt	5 mg 15 mg 30 mg	100 100 100	$15.90 $44.63 $91.00	$0.15 $0.45 $0.91
Roxicodone AAIPharma	5 mg 15 mg 30 mg	100 100 100	$26.49 $69.11 $133.18	$0.27 $0.69 $1.33
Morphine tablets Ranbaxy Ranbaxy Roxane	 10 mg 15 mg 15 mg	 100 100 100	 $26.61 $33.77 $13.58	 $0.27 $0.34 $0.14
MSIR Purdue	15 mg tab 15 mg cap 30 mg tab 30 mg cap	100 100 100 100	$18.08 $30.98 $30.55 $57.81	$0.18 $0.31 $0.31 $0.58
Hydromorphone tablets Various generic MNFs	2 mg 4 mg	100 100	$13.95 - $18.48 $20.95 - $30.47	$0.14 - $0.19 $0.21 - $0.31
Dilaudid® Abbott	2 mg 4 mg 8 mg	100 100 100	$41.01 $66.94 $121.84	$0.41 $0.67 $1.22

Source: First DataBank, Dec 2004.

2.25 Competitive Sales Force Size/Structures:

Sales Force Structure

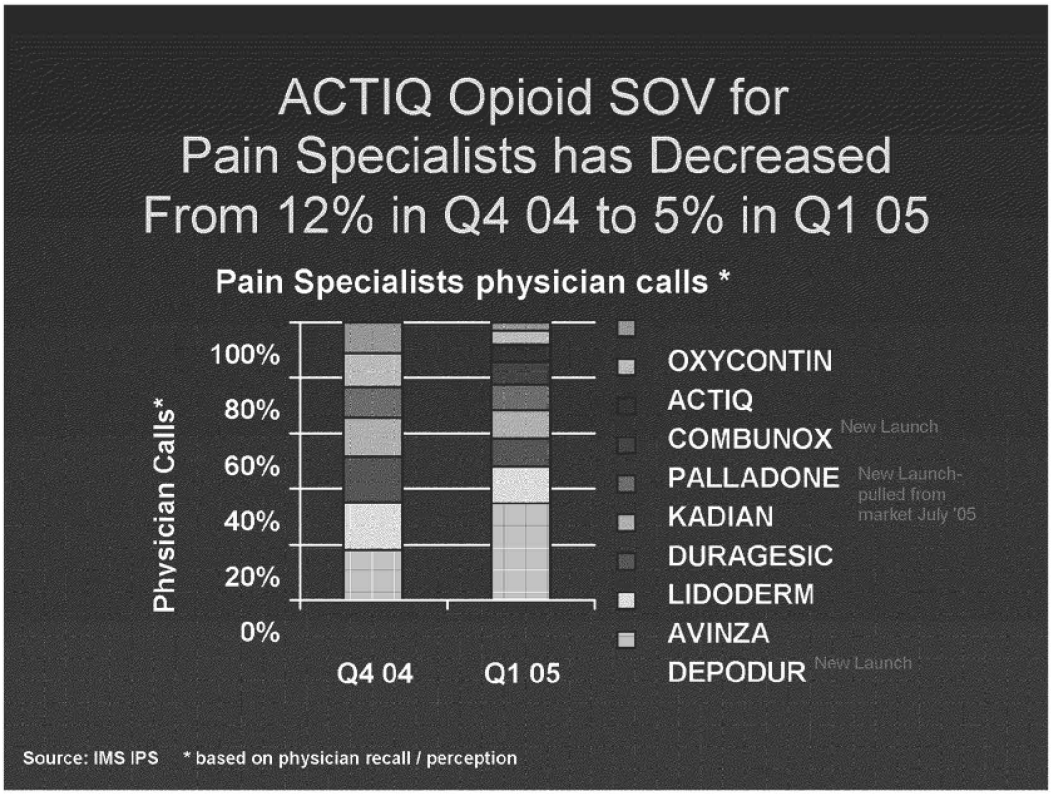
Pain Companies: Sales Force Structure
4Q04

COMPANY	SALES FORCE	# REPS	PROMOTED PAIN PRODUCTS
Purdue*	Pain Sales Force	550	Palladone, OxyContin, Senokot
Endo	Pain Specialty	70	Lidoderm, Percocet
	Community-Based Physicians	166	Lidoderm, Percocet
	Hospital	70	Depodur
J&J	Janssen Green	339	Duragesic, Ultracet
	Janssen Elder Care	283	Risperdal, Razadyne, Duragesic
	Janssen Hospital	106	Duragesic, Razadyne, Risperdal, Aciphex
	J&J Long-term Care	20	Risperdal, Levaquin, Duragesic
Organon/Ligand	Primary Care	550	Avinza, Remeron Soltab, Nuvaring, Cylcessa, Desogen, Mircette
	Hospital	95	Zemuron, Avinza, Nuvaring
	Specialty	180	Avinza, Remeron Soltab
Forest**	Forest Therapeutics (Mainly PCPs)		PCPs calls: Combunox in second or third position Pain Specialist/Orthopedic Surgeon (minority targets) calls: Combunox in first position
	Forest Ethicare (Mainly PCPs)		PCPs calls: Combunox in second or third position Pain Specialist/Orthopedic Surgeon (minority targets) calls: Combunox in first position
Watson	Urology	110	Oxytrol, Androderm, Reprexain
	Primary Care	160	Oxytrol, Androderm, Reprexain
	Managed Care	12	
Cephalon	Single Sales Force	430	Redaction - Other Teva Product ACTIQ
	Pain Care	100	ACTIQ and FEBT 4Q05

Source: Verispan 4Q 2004.
* Purdue laid off ~70% of their sales force following the withdraw of Palladone.
** Forest information from Forest CEO Wall Street Conference.

Pain Companies

The major companies in the pain market currently marketing branded pain medications (ie, not devices, not generics) include Janssen (Duragesic), Organon/Ligand (Avinza), Forest (Combunox), Alpharma (Kadian), and Endo (Lidoderm and Depodur). These companies have primarily focused on the outpatient chronic pain market. Purdue Pharma is no longer a major player in the pain market as the OxyContin patent has expired and Palladone has been withdrawn from the market.

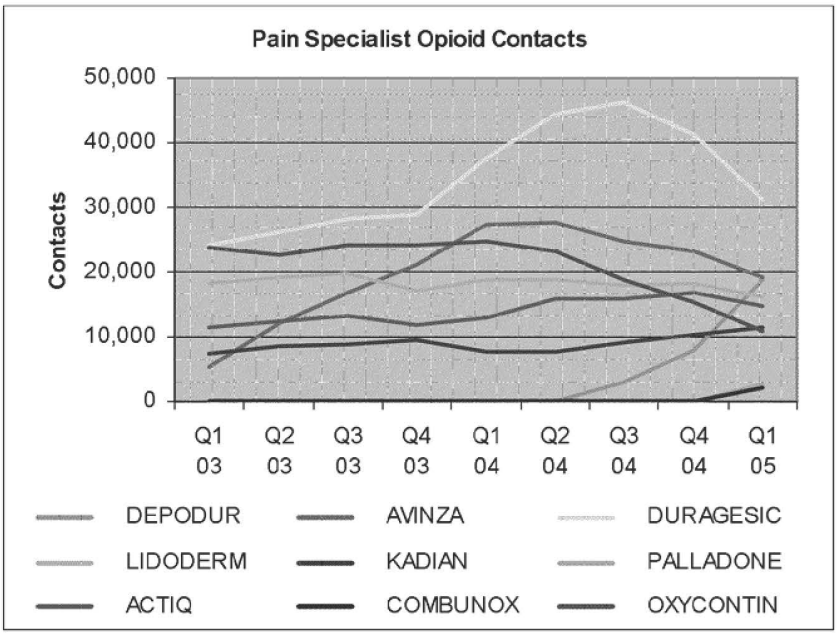


As seen in the graph above, physician contacts for older products facing generic competition are declining, while detailing on new products is gradually increasing. The decline in details based on generic competition as well as the withdraw of Palladone has created a window of opportunity for Cephalon; however, this window will be short-lived as additional products are expected to come to market. *(The FDA asked Purdue to withdraw the product from the market over safety concerns regarding its interaction with alcohol.)* Currently only Cephalon is conducting any significant level of promotional activity in the pure SAO market. With new pure SAOs on the horizon, maintaining a strong presence especially among pain specialists is imperative if Cephalon is to be perceived as a leader in the overall pain market.

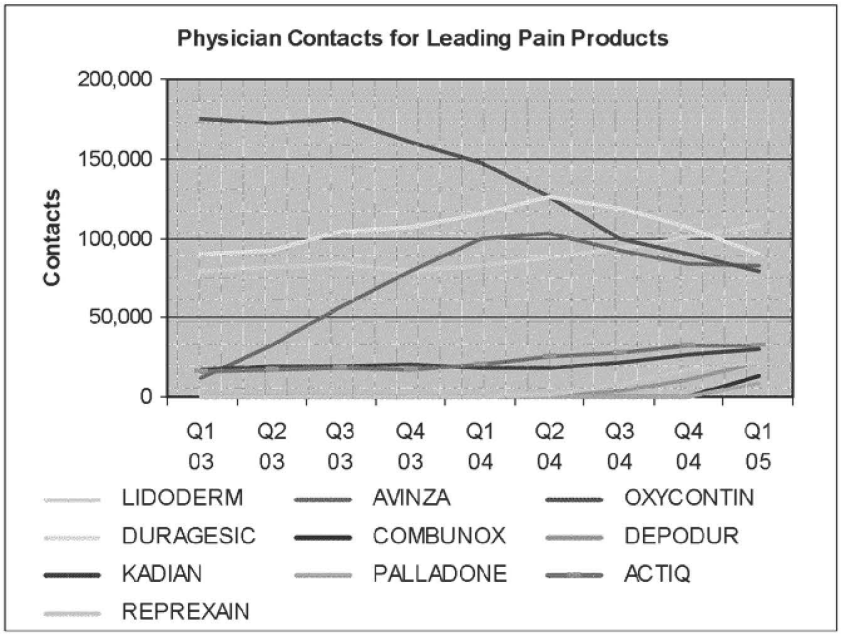
- ACTIQ is the only pure SAO actively promoted pain product but the overall opioid market is changing rapidly
  - Decline in promotion of leading LAOs (Duragesic, OxyContin)
  - Avinza has greatly increased physician contacts over the last 2 years
  - Combunox will be an interesting product to watch considering promotional claims around rapid onset and duration of effect
- Endo has become the share-of-voice (SOV) market leader, producing the greatest number of physician contacts in Q1 '05
  - Lidoderm (indicated for neuropathic pain of postherpetic neuralgia) occupies the primary position for the sales force creating the lion share of attention and focus
- Additional recently launched Opioids
  - Combunox (Forest – Oxycodone/Ibuprofen)
  - Reprexain (Watson – Hydrocodone/Ibuprofen)
  - DepoDur (Endo – Liposome injection Morphine Sulfate XR)
- Purdue was in the process of refocusing their promotional efforts from OxyContin to the newly launched Palladone (controlled-release hydromorphone); however, this product

was recently withdrawn from the market. Subsequently Purdue has laid of the majority of their pain sales force.

Physician Contacts by Brand



Source: *IMS Health*, IPS.



Source: *IMS Health*, IPS.

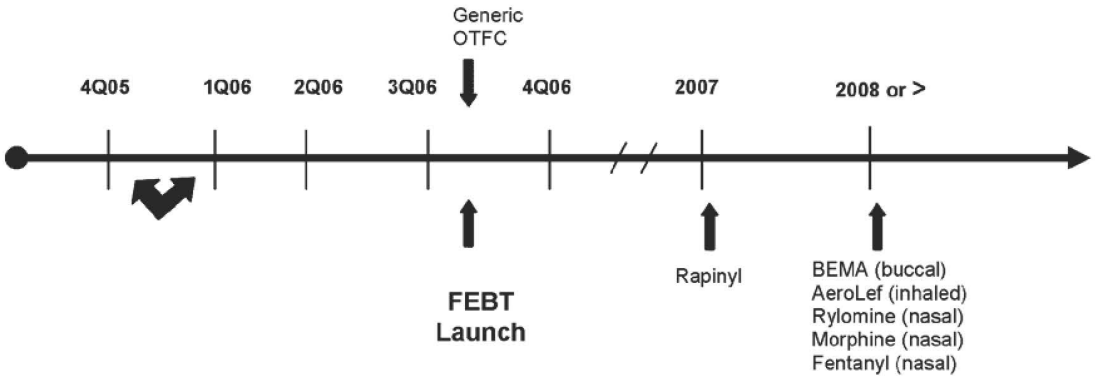
2.26 Future Competition

The most significant competitor for FEBT at launch will be Barr's generic OTFC. The next most significant competitor if/when approved will be Endo's Rapinyl.

In the moderate-to-severe pain market there are a number of products in development that may be competitors to FEBT. These products are displayed in the table below.

Drug Name / Dev. Co. Technology	Comments
Oxymorphone IR / Endo Immediate-release formulation of oxymorphone	Received approvable letter but at the request of the FDA is running a supplemental safety trial due to agency concerns of abuse related to the IR formulation. Product is expected to launch in 4Q '05 or 1Q '06. Endo is expected to launch IR & ER formulation as a package with ER for maintenance and IR as initial dose and for occasional pain flares.
Generic OTFC / Barr	Sugar-free formulation expected to launch upon FDA **approval** of FEBT. Of note, Barr has the right to purchase product from Cephalon so they could purchase sugar-free OTFC if Cephalon launches this formulation.
Rapinyl / Endo Sublingual fast-dissolving fentanyl wafer	Currently pursuing Phase III trials. Phase II trials were for breakthrough cancer pain (BTP). Medical Affairs from Endo reports that they will be pursuing an expanded nonmalignant BTP label after they launch the drug for BTCP. Endo mgt. has stated this product will be a direct "attack" on ACTIQ. Estimated launch 2007.
BEMA Fentanyl/BDS Biodegradable buccal wafer consisting of an adhesive layer and drug delivery layer	Currently seeking a partner for Phase III studies which are scheduled for 2H of 2005. Small drug-development company with limited resources. Phase II studies were completed with BTP cancer patients. Reported to dissolve in 20 minutes. Company presentation to investors projected price $5-6 per dose
AeroLEF/Delex Inhaled aerosolized liposome-encapsulated formulation of fentanyl citrate	Phase II in Canada, developed to provide needle-free delivery by inhalation. Company is claiming a rapid onset of action comparable to intravenous (IV) administration and sustained analgesia (12 hrs). Pursuing indications in Cancer and Post-operative pain.
Rylomine/Intrac,fka IDDS Morphine formulation	Phase II, intranasal delivery system, stated treatment is being developed for acute pain.
Morphine gluconate/Nastech	Phase II, intranasal delivery system, breakthrough pain indication
Fentanyl/West Pharma.als	Phase II, nasal delivery system, cancer pain

Estimated launch dates for potential BTP therapies

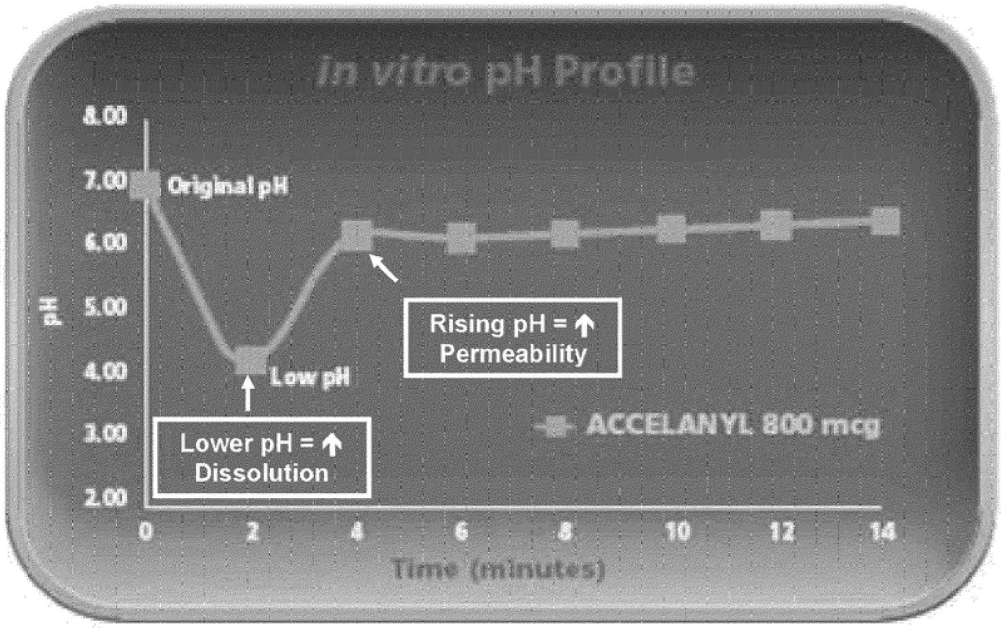


3 Product Overview – FEBT

3.1 Product Description

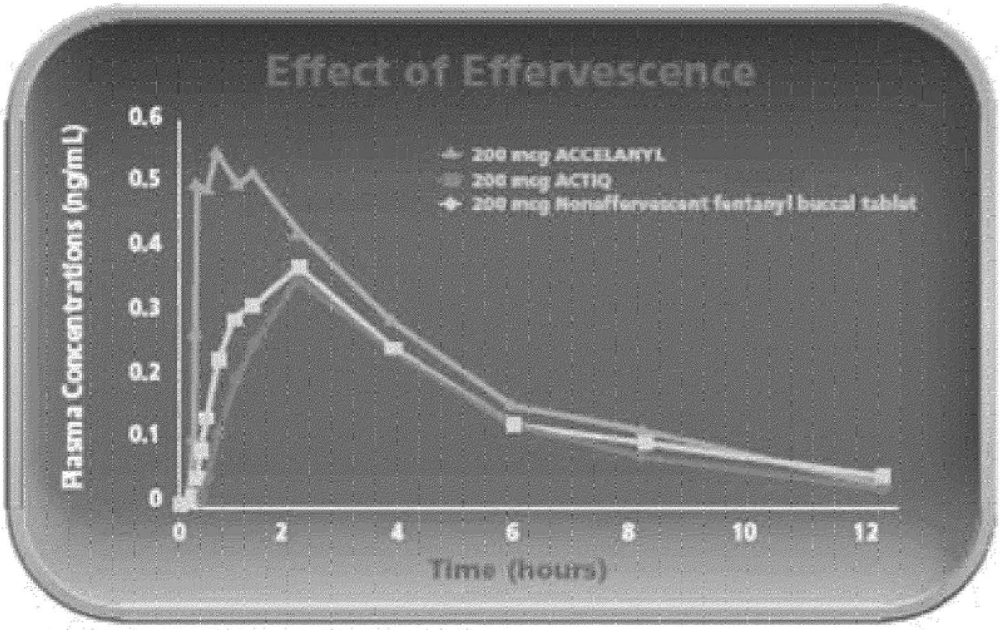
FEBT is a potent, rapid-onset opioid analgesic, intended for buccal mucosal administration. FEBT is formulated as a flat-faced, round, beveled-edge tablet. FEBT should be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and rapid absorption of fentanyl across the oral mucosa.

FEBT employs the OraVescent® drug-delivery technology, which utilizes an effervescent reaction to enhance the rate and extent of fentanyl absorbed through the buccal mucosa. It is believed that transient pH changes accompanying the effervescent reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH). Absorption may also be influenced by other changes thought to occur as a result of the effervescent reaction, including thinning of the epithelial layer and loosening of intracellular tight junctions.



The OraVescent method of delivery has distinct advantages over OTFC:

- Improved rate & extent of absorption, ie, higher & earlier systemic exposure
  - Greater absorption through oral mucosa (48% vs 22%)
  - Greater absolute bioavailability (65% vs 47%)
- More discreet & user-friendly drug delivery
- Simplified titration scheme
- Higher early systemic exposure



Pather SI, et al. *Drug Deliv Technol.* 2001;1.

Ultimately, FEBT is a more efficient delivery technology incorporating an effervescent reaction that improves the rate and extent of fentanyl absorption across the oral mucosa. The benefit to the patient is rapid onset analgesia.

3.2 Target Product Profile

This target product profile is based on the inclusion of data from the 2 pivotal efficacy BTP in cancer patient trials (099-14), the 2 safety trials (099-15 and 099-16), and 6 pharmacokinetic trials (099-11, 099-18, 1026, 1027, 1028, 1029). As of this date it is assumed the NDA submission for BTP in cancer patients will not include the second BTP efficacy trial, 3039. Without the 3039 data the FEBT Target Product Profile efficacy section is the same as ACTIQ. A sNDA with the 3039 data is expected to be filed immediately after approval.

Target Product Profile
Indication
At launch: Management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain

Formulation & Delivery Platform: Sugar-free & flavor-free orally dissolving tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

- Passive drug delivery (simply place next to buccal mucosa – dissolves without actively moving the tablet around in the mouth)
  - Nonirritating to buccal mucosa in majority of patients
  - Predictable drug delivery (less chance for user error vs ACTIQ)
- Multiple strengths for efficient and convenient dosing titration

Administration: Place the tablet between the cheek and gum (dwell time 15 minutes)

Efficacy	
FEBT vs placebo	• Statistically significant mean pain-intensity difference (PID) over time: 15, 30, 45, and 60 minutes • Statistically significant mean pain relief (PR) over time: 15, 30, 45, and 60 minutes • Statistically significant mean total pain relief (TOTPAR) over time: 15, 30, 45, and 60 minutes • Statistically significant mean summed pain intensity difference (SPID) over time: 15, 30, 45, and 60 minutes • Statistically significant pain relief for up to 60 minutes • Statistically significant portion of patients rate FEBT "good" on global assessment of drug performance scale at 30 and 60 minutes
ACTIQ to FEBT	• Clinical data to support safe switching dose recommendation from ACTIQ to FEBT

Pharmacokinetics

- T_{max} = 47 minutes
- Dose proportionality for AUC, C_{max} for all strengths
- Dose proportionality up to 600 mcg on T_{max}
- Efficient drug delivery: 65% absolute bioavailability as compared to ACTIQ (47%)
- FEBT demonstrates higher early systemic exposure ($AUC_{0\text{-}tmax}$ and C_{max}) as compared to ACTIQ
- Greater portion of FEBT absorbed primarily via the buccal mucosa (48%) as compared to ACTIQ (22%)

Safety & Tolerability

Adverse events are typical opioid side effects that generally cease or decrease with continued use of the drug.

The most serious adverse event associated with opioids are respiratory depression, circulatory depression, hypotension, and shock.

How Supplied
Individual child-resistant blister packages Perforated blister card consisting of 4 individually packaged tablets Box containing 7 blisters cards (28 total tablets per box)
SOURCE DATA
This profile is based on the inclusion of the following: • PK trials: 099-11, 099-18, 1026, 1027, 1028, 1029 • Pivotal efficacy trials: 099-14 • Safety trial: 099-15, 099-16

3.3 Dosing

- All patients need to be opioid tolerant.
- All patients should start on 100 mcg with the exception of patients previously receiving ACTIQ:
  - Tablet should be placed in the buccal cavity (above a rear molar between the upper cheek and gum) until disintegrated
  - Usually takes ~14-25 minutes; if after 30 minutes remnants remain, they may be swallowed with a glass of water
  - Swallowing results in lower peak concentrations
  - Re-dosing within a single episode:
    - 30 minutes after start of previous tablet
    - Same dosing strength should be used
  - Increasing the dose:
    - From the initial dose, patients should be closely followed and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with minimal side effects
    - Dosage strengths should not be skipped
    - Patients should record use over several episodes of BTP and discuss with physician to determine if a dosage adjustment is required
    - Multiple tablets may be used to produce mcg equivalents to available doses
- For patients switching from OTFC to FEBT, the starting dose should be initiated as shown below:

Current ACTIQ dose (µg) per BTP Episode	FEBT Initial Titration Dose (µg)
200	100
400	100
600	100
800	200
1200	400
1600	600

3.4 Strengths

At launch: FEBT tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

Currently a 300-mcg tablet is in development. This strength is expected to be available postlaunch (sNDA submitted within first year of launch). In addition, a higher dosage strength (potentially 1200 mcg) is also being considered for development as a result of the lack of dose proportionality between 1600 mcg of ACTIQ and 800 mcg of FEBT.

3.5 Clinical Performance to Date

To date, 6 PK studies (099-11, 099-18, 1026, 1027, 1028, 1029) have been completed. Data from these trials are presented in Appendix 3. Below are the available key results from these trials:

- T_{max} = 47 minutes
- Dose proportionality for AUC, C_{max} for all strengths – up to 800 mcg
- Dose proportionality up to 600 mcg on T_{max}
- Efficient drug delivery: 65% absolute bioavailability as compared to ACTIQ (47%)
- FEBT demonstrates higher early systemic exposure ($AUC_{0\text{-}tmax}$, and C_{max}) as compared to ACTIQ
- Greater portion of FEBT absorbed primarily via the buccal mucosa (48%) as compared to ACTIQ (22%)

The single efficacy trial (099-14) that will be included in the NDA is completed. In the 099-14 trial, FEBT demonstrated superiority versus placebo at all time points (15, 30, 45, and 60 minutes) for SPID, PID, PR, and TOTPAR. FEBT was superior to placebo in the Global Assessment of Drug Performance at 30 and 60 minutes. In this study when patients received a placebo tablet they were twice as likely to require rescue medication as when they received FEBT. See Appendix 3 for presentation of the 099-14 trial results.

Note: Again, the 3039 cancer BTP efficacy study yielding differentiating onset of action data will not be included in the NDA. However, it will be published prior to launch and submitted with the 3042 (back BTP) study immediately following launch.

For details on the development program see the attached FEBT Development Plan (Appendix 3)

3.6 Product Labeling Considerations

As the Phase III data become available the results will be interpreted and inserted into the proposed draft label. It is assumed that the FDA will require the FEBT label to contain similar elements to the ACTIQ label.

The following is a list of the minimum FEBT label requirements to be competitive in the BTP marketplace:

1. **Description**
   - Include information about the effervescent delivery platform —> all CO_2 effects
   - Discuss ease of use and "passive" application of discreet tablet
2. **Clinical Pharmacology**
   - Need to include OTFC to FEBT switching data (conversion chart for safety)

3. Pharmacokinetics: Bioavailability and Absorption

- Venous vs arterial blood test issue
- Include relative bioavailability study
- T_{max} and C_{max} data clearly illustrated
- Dose proportionality clear explanation
- Efficient delivery of fentanyl via OraVescent delivery technology
- Multiple-tablet dosing approximately equals single-tablet PK of same microgram (mcg) equivalent
- Comparison of T_{max} for FEBT and OTFC

4. Pharmacodynamics: Distribution, Metabolism, and Elimination

- Appropriate supporting data

5. Clinical Trials

- Describe the clinical trial
- Based on the pre-NDA meeting it is questionable how many secondary endpoints may be included in the label

6. Indications and Usage

Launch

At launch the expected indication will be limited to BTP in cancer patients (similar to ACTIQ) as only the pivotal 99-14 efficacy data, 99-15 open-label safety data, and data from the 5 PK studies will be included in the initial NDA.

- FEBT is indicated for the management of BTP in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. Patients considered opioid tolerant are those who are taking at least 60 mg oral 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
- Because life-threatening respiratory depression could occur at any dose in non–opioid-tolerant patients, FEBT is contraindicated in the management of acute or postoperative pain. Because FEBT has not been studied in non–opioid-tolerant patients, this product must not be used in non–opioid-tolerant patients
- Patients and their caregivers must be instructed that FEBT contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. (See Information for Patients and Their Caregivers for disposal instructions.)

Postlaunch

Immediately following approval, a label supplement containing data from the 3039 trial will be submitted to the FDA. It will be described in the *Clinical Trials* section. Efficacy charts depicting earlier onset data from this trial should replace any 099-14 efficacy charts. Timing for a label change review is typically 6 months. Failure to include this differentiation data at launch may adversely effect the immediate uptake of FEBT postlaunch.

Note: Rapid onset claims from the 3039 study will be included in promotional launch material pending preclearance. These data are anticipated to be published prior to launch and submitted as a label supplement immediately following launch.

Additional clinical trials are being conducted with the objective of expanding the label beyond BTP in cancer patients. Based on guidance from the FDA regarding the need to perform toxicology and carcinogenicity studies, it is anticipated that this label enhancement would occur no sooner than Q1 2009 postlaunch. Data from these trials are expected to be available at launch via publications and Medical Affairs Department inquiries.

Below is the optimal anticipated FEBT Package Insert "INDICATION AND USAGE" section based on the additional clinical trials in for BTP in chronic low back pain and neuropathic pain.

- FEBT is indicated for the management of BTP in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. Patients considered opioid tolerant are those who are taking at least 60 mg oral 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.
- Because life-threatening respiratory depression could occur at any dose in non–opioid-tolerant patients, FEBT is contraindicated in the management of acute or postoperative pain. Because FEBT has not been studied in non–opioid-tolerant patients, this product must not be used in non–opioid-tolerant patients.
- FEBT is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

7. Adverse Events

- Separate table of AEs for ACTIQ conversion portion of the efficacy trial

8. Abuse and Potential Dependence

- Limited to "opioid class" language

9. Dosage and Administration

- No quantity-limit mention in this section (1 box of 28 tablets should be sufficient to initiate a patient and titrate to an effective dose)
- Include statement on approximate dose equivalency
- Allow for multiple tablet dosing

10. How Supplied

Individual child-resistant blister packages. The blister cards will most likely contain 4 tablets but this decision is not final. If the final decision is 4 tablet cards then the final packaging box will contain 7 blister cards (28 doses per box). All strengths will be packaged similarly.

3.7 Price

A pricing study will be initiated in 4Q '05. This study, along with research with TPPs planned for 3Q through 4Q '05, will provide input to develop the pricing strategy for FEBT.

3.8 FEBT vs. ACTIQ Points of Differentiation

FEBT	ACTIQ
Indication	
• Launch indication in BTP in cancer patients • Life cycle strategy to expand label to noncancer BTP • Phase III trials in neuropathic pain (3041) and low back pain (3042) to be completed, published prior to product approval	• BTP cancer-only indication limits promotional ability • Cancer-only indication allows MCOs and Medicaid to more easily restrict reimbursement • Minimal data to support use beyond BTP in CA
Efficacy	
• Onset of analgesia 15 minutes (099-14 trial) • 3039 trial is designed to measure pain relief as early as 5 minutes • It also uses stopwatch to measure onset of meaningful pain relief	• Earliest time point measured was 15 minutes o "Pain relief in 15 minutes, but may not experience full relief for up to 45 minutes" • ACTIQ median time for pain relief 4.2 minutes (Lichtor et al 1999), but not in label
• Duration of analgesia – being measured up to 60 minutes (3039 trial measure out to 120 minutes)	• Only measured versus placebo up to 60 minutes
Pharmacokinetics	
• More efficient delivery of fentanyl • Increased bioavailablity o Less chance for user error versus ACTIQ (passive versus active consumption) o PK data: 65% absolute bioavailability vs ACTIQ 47% o Greater portion of FEBT absorbed by the mucosa (48%) as compared to ACTIQ (22%)	• 50% bioavailability but must concede that "longer or shorter consumption times may reduce efficacy" o Longer or shorter consumption times can be a result of "user error" and provide inconsistent delivery of fentanyl via the oral mucosa and thus efficacy
Secondary Efficacy Data	
• No improved patient function/QOL data	• No improved patient function/QOL data
• HEOR data expected to be available for dissemination	• None available promotionally o One small retrospective study of cancer patients done at MD Anderson showed promising results
• No clinical trial data on patient preference – (FEBT) versus ACTIQ or other previous SAO medication	• There is a MSIR vs ACTIQ study but Cephalon is unable to use it promotionally
Dosing and Administration	
• Ease of dosing and titration o Simpler & more efficient titration scheme vs ACTIQ (less costly) o Expect most patients to be able to titrate to "effective dose" using 1 box of 100-mcg tablets o Expecting no quantity limit on titration prescription size o Data showing multiple lower strength tablets ≈ 1 higher strength o Expect to have ACTIQ to FEBT dose conversion chart in label o Potential inclusion of an equianalgesic chart in label or via a publication for safety support – prevent equal dose conversion	• Perceived cumbersome titration process o Perceived weaknesses ▪ No equianalgesic dosing chart for ACTIQ exists ▪ Should prescribe 200 mcg as first Rx (despite same safety when randomized to start at 400 mcg in clinical trials) ▪ Should prescribe only 6 units in all titration Rx's until maintenance dose found • Causes problems at pharmacy – don't want to break boxes • Causes inconvenience – multiple office visits,

FEBT	ACTIQ
from OTFC to FEBT	Rx's and thus co-pays ▪ Should only titrate up 1 strength level at a time – should not "jump strengths" • Limits flexibility and causes inconvenience for patient (multiple Rx's and co-pays) and prescriber (office visits)
• Small tablet that is placed between upper gum and cheek – discreet administration • More convenient formulation • Ease of use	• ACTIQ is a much larger lozenge on a stick – more obtrusive and noticeable by others • ACTIQ requires a lot of clinician and patient education about proper consumption technique • It is an active, 15-minute process and forces the patient to "apply" the drug instead of simply "taking it" like a pill o This process allows for user error (too much sucking and swallowing – not enough oral mucosal absorption) and thus less reliable results • "Longer or shorter consumption times may impact efficacy."
OTHER	
• Less chance for accidental exposure to children o Less possible to have "partially used units" left around like ACTIQ o No handles to dispose of (with drug remaining on handle)	• Handles with drug remaining on them may pose a risk of accidental ingestion by children
• Packaging allows physician to monitor patient usage by requesting patient save and bring the individual blister container to office for counting/monitoring purposes	• Physicians can monitor patient usage by doing stick counts

Attribute Summary

FEBT is expected to have clinical data to support rapid onset of analgesia (5-15 minutes) and duration of pain relief measured up to 60 minutes; however, the 3039 study with this differentiation data will only be submitted in an sNDA immediately following launch. In addition, it is anticipated that FEBT may provide more predictable bioavailability and greater dosing convenience compared to ACTIQ.

FEBT is expected to be at a disadvantage in regard to reimbursement vs pure and combination SAOs because of pricing. Until a pricing strategy is determined it is not clear how FEBT will compare to ACTIQ.

The table below is an initial attempt to summarize the projected FEBT performance vs currently marketed competitors. It will be critical to evaluate these areas in market research to better understand the core attributes of FEBT.

Efficacy	****	****	****	***
Efficacy – Onset of Action	***	***	**	**
Efficacy – Duration of Effect	***	***	****	****
Tolerability	***	***	***	***
Convenience (formulation)	***	*	****	****
Safety – Perceived Abuse Potential/Diversion	*	*	**	***
PK/PD – Bioavailability (efficient delivery)	****	**	***	***
Price	**TBD**	*	****	****
Formulary Availability/Reimbursement	**N/A**	*	****	****

Notes: 1) This table is a summary of the findings outlined within this document only. It is not informed by any clinical or market research other than what is contained within this document. 2) FEBT ratings based on predicted clinical profile.
Key: * = disadvantage; **** = advantage

3.9 FEBT SWOT Analysis

• Onset of analgesia vs placebo <15 minutes
• Duration of analgesia measured up to 120 minutes
• Discreet and convenient dosing formulation
• Efficient drug delivery
  o 65% absolute bioavailability
  o 48% via buccal mucosa
• Simplified titration scheme
• Data & conversion chart for ACTIQ to FEBT switch
• Clinical program to expand label; data expected in neuropathic and low back pain
• Patent on FEBT through 2019
	• CII-abuse and diversion potential
	• Efficacy data in label does not differentiate FEBT from ACTIQ
	• Cost vs SAOs (branded and generic alternative therapeutic options)
	• Limited label (BTP in cancer patients) at launch
	• Perceived safety concerns of ROO
	• Misunderstanding of fentanyl potency and equianalgesic conversion (mg vs mcg)
	• Anticipated reimbursement restrictions
	• Cephalon not a lead player in pain market

• KOL eagerness to evaluate and establish standards for treatment guidelines for BTP • Increased focus on pain management from JCAHO (fifth vital sign) and NIH (decade of pain control and research) • Though limited there is some increasing awareness and understanding of BTP • Concentrated ACTIQ prescriber base enables for focused targeting • Limited number of promoted products within the market segment • Aging population growth • Opportunity to develop HEOR data for BTP (burden of illness)	• Limited understanding of BTP and its appropriate management • Fear of abuse and diversion with opioids • Increasing government restrictions on CII opioids • Pure SAO market 100% generic • Generic OTFC available prior to launch • Published data for ACTIQ vs IV morphine documenting median time for pain relief 5 minutes • Limited formal training in pain management in medical school/residency programs • Managed Care hurdles increasing to restrict high-cost drug use • No inclusion of FEBT in treatment guidelines • Emerging ROO pain formulations (eg, Rapinyl)

4 FEBT Marketing – Strategic

4.1 Commercial Vision

The commercial vision is to establish FEBT as the optimal choice for BTP.

- **Short-term (Market Conditioning):** Build market anticipation for FEBT by clearly differentiating FEBT based on its unique delivery platform and combination of patient benefits, which include rapid onset of analgesia, predictability, and ease of use.
- **Middle-term (Year 1):** Establish FEBT as the optimal choice for BTP in cancer patients. The initial focus will be to convert ACTIQ loyalists to FEBT adopters, with the goal of switching ACTIQ patients and driving new patient starts with this existing prescribing base. This focused approach will then evolve to expand the market by adding new prescribers. In addition, appropriate educational and feedback mechanisms will focus on expanded use beyond BTP noncancer.
- **Long-term (Years 2 and beyond):** Solidify FEBT as the optimal choice for the treatment of BTP.

4.2 Positioning

The following is the FEBT positioning statement based on the 2005 positioning market research study and the anticipated FEBT product profile:

FEBT is the first and only fentanyl buccal tablet, which utilizes an effervescent reaction to provide the most rapid onset of analgesia of any oral opioid resulting in improved patient functioning and activities of daily living.

4.3 Preliminary Supporting Messages (in development)

Qualitative market research will be initiated in early 4Q05 to develop, design, and test potential messages and supporting claims. The quantitative market research phase will follow in 1Q06 to select the optimal messages platform. Below are potential messages based on the anticipated product profile:

Rapid onset of pain relief for BTP

- *Unique OraVescent® delivery technology enhances the rate and extent of absorption of fentanyl providing fast, convenient BTP relief in cancer patients*
- *15-minute onset of action addresses the unpredictable urgency of BTP*
- *Proven coverage of pain up to 60 minutes*
- *Simple to administer dosing formulation*
- *Passive administration; simply place tablet between cheek and gum and allow to dissolve*
- *Discreet dosing administration compared to ACTIQ*

Flexible dose range provides step-up pain relief without concern

- *Dose proportionality between dosage strengths (AUC)*

Predictable drug delivery ensures appropriate use

- *Simple passive OraVescent delivery ensures less administrative error*
- *48% of fentanyl directly absorbed through the oral mucosa*

- *65% absolute bioavailability*

Safety

- *Side effect profile similar to other SAOs*
- *Risk MAP available to aid in appropriate patient selection to minimize risk for abuse, addiction, and diversion*
- *Cephalon supports educational initiatives (ESP) to help minimize risk for abuse, addiction, and diversion of opioid medications*

4.4 Key Issues

Key marketing issues Cephalon must effectively address include the following:

- **Absence of Time to Convert Prescribers (generic ACTIQ available prior to FEBT launch)**
  The most significant marketing issue that Cephalon will face with FEBT is driven by the agreement with the FTC, allowing Barr Laboratories to market a generic OTFC upon FEBT final approval. The proven industry practice has been to drive product switches prior to the introduction of a generic alternative, optimally 12-18 months prior to loss of exclusivity. A successful conversion from the original product to a successor compound is largely dependent on the following variables:
    - **Adequate time to establish the successor brand prior to the availability of the generic version of the precursor brand**
    - Level of clear and meaningful differentiation between the precursor and the successor
    - Total level of promotional resources/share of voice applied
    - Dedicated, sophisticated and optimally sized sales force with the successor brand in the primary selling position
    - Comprehensive managed care strategy to drive favorable reimbursement
    - Extensive patient database that will enable DTP (Direct to Patient) correspondence

  Unfortunately, Cephalon will not have the opportunity to address the most important variable in securing a successful switch – sufficient time to convert ACTIQ loyalists prior to generic availability. It is expected that Barr will launch a generic OTFC at least 30 days prior to the launch of FEBT. Retail pharmacies will update their systems for a generic OTFC alternative as soon as it becomes available. Most health plans have mandatory generic substitution policies and therefore it is predicted that the majority of ACTIQ prescriptions may be substituted. In addition, in an effort to control costs health plans may establish prior authorization and/or step edits to limit FEBT usage.

  Furthermore, prescriptions for CII products may not be refilled. Patients must see their prescribing physician on a monthly basis to receive their next CII prescriptions. As a result of this, there is an opportunity to convert ACTIQ loyalists to FEBT before generic OTFC becomes firmly entrenched in the market.

  Ultimately, the lack of switch time, the immediate generic availability, and the anticipated erosion rate make the time period prior to launch and immediately following the FEBT launch (30-90 days) critical to the success of the product. To support a successful conversion of ACTIQ loyalists to FEBT adopters, it will be necessary to focus on the remaining variables that drive successful switches. Prior to launch it will be imperative to secure sufficient resources and initiate appropriate market conditioning educational tactics. This will help clearly differentiate FEBT and facilitate brand

awareness/anticipation among ACTIQ loyalists. It will also be critical to establish a comprehensive managed markets strategy and identify the optimal size, structure, and timing for the implementation of a well-trained Pain Care sales force. Immediately postlaunch, within the first 30-90 days, it will be crucial to implement a focused Loyalists conversion strategy.

- **Limited Ability to Differentiate From ACTIQ at Launch**
  At launch the FEBT label will be based on 1 pivotal clinical efficacy trial, the 99-14 trial. The primary end point of this trial was pain relief beginning at 15 minutes postdosing. This trial design is identical to the ACTIQ pivotal trials. Cephalon is conducting a second clinical efficacy trial in cancer patients with BTP. This trial (3039) is designed to differentiate FEBT from its competitors based on its speed of action. This study measures onset of pain relief as early 5 minutes and time to meaningful pain relief as measured by stopwatch. This trial will not be completed in time to be included in the initial FEBT NDA. It will be submitted as a label change immediately following approval.

  Note: Rapid onset claims from the 3039 study will be included in promotional launch material pending preclearance. These data are anticipated to be published prior to launch and submitted as a label supplement immediately following launch.

- **Significant Resources Required to Effectively Prepare and Launch FEBT**
  In order to effectively launch FEBT and convert ACTIQ loyalists, Cephalon will need to allocate significant budgetary and personnel resources for FEBT prelaunch and launch activities which include but are not limited to
  - Market conditioning to establish a new, emerging class of opioids (ie, ROOs)
  - Comprehensive managed care initiative
  - Medical education around BTP awareness (assessment and treatment)
  - Dedicated pain franchise personnel from supporting internal departments to ensure timely NDA approval, promotional materials availability, optimal label, and Risk MAP
  - Clinical development opportunities for Phase IIIb & IV studies

  In addition to securing sufficient resources, it will be critical to gain consensus of resource utilization among internal departments.

- **Anticipated Unfavorable Reimbursement Status**
  Third Party Payers (TPPs) are expected to continue to drive business to generics when available and to place restrictions on premium-priced products. It is anticipated that FEBT will be premium priced. Status of TPP reimbursement of FEBT will have an impact on the success of the brand. Potential barriers utilized by TPPs to limit access may include the following; prior authorizations, usage/quantity limits, step/edit treatment requirements, and tiered co-pay structures. The development of a comprehensive managed-markets plan must be completed well in advance of the launch of FEBT to minimize these potential barriers and support access for appropriate patients. The core elements of a comprehensive managed care plan include
  - Situation analysis
  - Strategies to secure favorable reimbursement
    - Document the burden of illness
    - Develop value proposition for the product
    - Determine scenario pricing and contracting strategies
  - Tactics

- **Limited Awareness and Understanding of Appropriate Diagnosis and Treatment of Breakthrough Pain (BTP)**
  The majority of physicians believe that they are managing chronic pain adequately; however, based on market research and feedback from consultants/advisors, there appears to be a lack of understanding among many physicians about the characteristics (eg, rapid onset and relatively short duration of pain), appropriate diagnosis, assessment, and effective treatment of BTP. Many physicians fail to recognize BTP as a distinct component of chronic pain, separate from the persistent pain experienced by the majority of chronic cancer and non–cancer pain sufferers. A lack of treatment guidelines specific to BTP, minimal mention of BTP in cancer and noncancer chronic pain treatment guidelines, a lack of clinical data in the literature evidencing noncancer BTP, and limited education or formal training during medical school and residency may also be contributing factors. Ultimately, this lack of understanding of the characteristics and appropriate diagnosis of BTP among opioid-prescribing physicians negatively affects their choice of therapy. Most fail to realize the need for a rapid onset opioid, which may be the most appropriate choice for many patients suffering from BTP. It will be important to not only raise awareness of BTP (characteristics, assessment, and treatment) but also to clearly differentiate the advantages and risk profile of rapid-onset opioids (ROOs) from short-acting opioids (SAOs).

- **Limited KOL/Professional Society/Managed Care Relationships**
  Cephalon is not currently viewed as a market leader in pain. Cephalon has limited relationships with KOLs, managed care decision makers, and leading pain societies compared to other market leaders. It will be important for Cephalon to be viewed as a company committed to the pain community.

- **Challenging Selling/Marketing Environment Requiring Sophistication and Expertise**
  The pain market is very complex and constantly evolving. Because of the potential for abuse, addiction, and diversion, CII medications are subject to stringent DEA and state regulations that are complex for pharmacies and prescribers. These include recording requirements, use of triplicate prescriptions pads in some states, special storage, non–refillable prescriptions, and sampling limitations. For example, coupon sampling programs are prohibited in the state of New York.

  Another complexity is that the undertreatment of pain continues to be a widespread problem. It has been postulated that 1 reason why pain is undertreated is physician fear of prescribing opioid analgesic medications (ie, opiophobia). This fear is mostly attributed to concerns of abuse, addiction, and diversion, as well as scrutiny by regulators that monitor the prescribing and dispensing of these medications. Despite mounting evidence demonstrating that effective analgesia improves quality of life, this fear persists. In general, physicians try to balance fear of opioid abuse (addiction and diversion) and regulatory scrutiny with the patients need for medications that provide safe and effective analgesia while improving daily functioning and restoring quality of life.

  Finally, the FDA requires all newly approved schedule II opioid products to implement a comprehensive Risk Minimization Program that meets the standards set by the Guidance for Industry Development and Use of Risk Minimization Action Plans.

  All of the aforementioned factors contribute to the difficulty and complexity of selling/marketing a CII medication. In addition, Cephalon will again be marketing an opioid in a novel delivery system. As with ACTIQ, Cephalon will face challenges inherent to establishing a new delivery platform in a class dominated by oral tablet formulations.

Therefore, it is imperative for Cephalon to establish the appropriate size, timing, and structure of a Pain Care Sales Force as well as pain-dedicated Medical Science Liaisons. Ideally, a Pain Care Sales Force in place by Q4 '05 would allow for the development of sufficient therapeutic expertise and adequate rapport with ACTIQ loyalists by FEBT launch (Q3 '06) to effectively execute the conversion strategy.

4.5 Critical Success Factors

In order for Cephalon to continue to be successful in the BTP market post–ACTIQ patent expiration it must successfully convert ACTIQ loyalists to FEBT adopters and gain additional business from those physicians and patients who had not previously adopted ACTIQ. There are 7 critical success factors that must be addressed in order for FEBT business objectives to be achieved.

1. **Successfully convert ACTIQ Loyalists to FEBT Adopters within the 90-day period**

   In order for Cephalon to continue to be successful in the BTP market post–ACTIQ patent expiration it must successfully convert ACTIQ loyalists to FEBT adopters. Because Cephalon will not have time to convert ACTIQ loyalists to FEBT adopters prior to the availability of generic OTFC the focus will be to implement alternative, proven strategies to drive conversion within the crucial 30- to 90-day period postlaunch.

   Prior to launch, appropriate market conditioning initiatives will be implemented to create the necessary awareness and anticipation for FEBT. Special care will be taken to ensure no preapproval promotion of FEBT occurs. Prelaunch initiatives will establish the OraVescent delivery technology and Cephalon as a leader in the pain market. Other initiatives will allow FEBT to be clearly differentiated from ACTIQ and other medications used to treat BTP. In addition, during the prelaunch phase, Cephalon will create and have ready for execution at launch, high-impact promotional tactics/tools that will support the rapid conversion of ACTIQ loyalists to FEBT adopters. A Pain Care Sales Force will be in place by Q4 '05 to provide the opportunity to develop relationships and rapport with key target physicians prior to launch.

   Additionally, it will be critical that FEBT is available in pharmacies as soon as possible after final approval because of the availability of generic OTFC. Currently, although aggressive, it has been determined that FEBT can be available in pharmacies 21-30 days post–final FDA approval. At present, Chemistry & Manufacturing Control (CMC) is evaluating various options in order to minimize the time from approval to product availability in pharmacies (for example, manufacturing FEBT "at risk"). This is an area Cephalon must continue to examine in order to determine the earliest point FEBT will be available for appropriate patients.

   At launch, Cephalon will begin driving conversion of ACTIQ loyalists to FEBT adopters by leveraging strong relationships and bridging from the solid market conditioning base it established pre-launch. Focused marketing and sales execution will encourage trial and usage of FEBT by ACTIQ loyalists.

2. **FEBT is clearly differentiated from ACTIQ and other BTP treatment options**

   To be successful FEBT must be clearly differentiated from ACTIQ and other options for BTP treatment (eg, SAOs, and other ROOs to be launched in the future). The following product attributes will allow for FEBT to be clearly differentiated:

- Unique effervescent delivery system allowing for the rate and extent of fentanyl absorption to be accelerated
- Rapid onset of analgesia
- Ease of use, convenience
- Predictable pharmacokinetics and pharmacodynamics
- Discreet, unobtrusive administration (no handle)

3. Sufficient resources are secured and aligned among internal departments

Sufficient resources must be secured across all functional departments (marketing, sales, RA, SciComm, MA, pubs, managed care, etc) to effectively execute pre- & postlaunch activities. It will be necessary to have adequate investment and resources to support the following:

- Clinical and Regulatory meet their milestones
- Implementation of marketing conditioning activities
  - Establish Cephalon as a market leader in pain
  - Establish awareness for OraVescent delivery technology
  - Increase awareness of BTP (characteristics, assessment, treatment, etc)
- Determination of the optimal size and structure of the sales force
  - Fully train and prepare a Pain Care Sales Force for launch
  - It is recommended that this sales force be in place by Q4 2005
- Negotiate optimal label which clearly differentiates FEBT (inclusion of 3039 study results)
- Negotiate optimal Risk MAP
  - Focus should be to minimize risk without compromising product growth in the appropriate patient population

4. Physicians and patients have access to FEBT

Achieving favorable reimbursement status will be critical for the success of FEBT. Because of an expected premium price for FEBT it is anticipated that TPPs will seek to limit usage by placing hurdles and restrictions on prescribing. In order to obtain favorable reimbursement Cephalon must do the following:

- Demonstrate the burden of illness associated with nonoptimal treatment of BTP
- Demonstrate a value proposition of FEBT and its impact on the burden of illness of BTP
- Establish opioid category of ROOs and clearly differentiate it from oral SAOs
- Provide appropriate resources to prescribers to overcome TPP barriers
- Apply appropriate resources to TPPs to gain optimal access for FEBT

Additionally, it will be critical that FEBT is available in pharmacies as soon as possible after final approval because of the availability of generic OTFC. Currently, although aggressive, it has been determined that FEBT can be available in pharmacies 21-30 days post–final FDA approval. At present, Chemistry & Manufacturing Control (CMC) is evaluating various options in order to minimize the time from approval to product availability in pharmacies. (For example, manufacturing FEBT "at risk"). This is an area Cephalon must continue to examine in order to determine the earliest point FEBT will be available for appropriate patients.

5. **Continue to develop BTP market by increasing awareness and understanding of BTP and its optimal treatment**

   Creating a high level of excitement and anticipation for FEBT will be essential to establishing FEBT in the market. The availability of generic OTFC at launch and the anticipated launch of Rapinyl® (Endo), another rapid onset fentanyl product in 2007, heightens the urgency to accelerate FEBT market penetration.

   In order to create excitement and anticipation of FEBT, Cephalon must increase physician understanding of BTP and its optimal treatment. By doing so, the market will more readily recognize the differentiating benefits of FEBT.

6. **Key Opinion Leaders support FEBT as an effective treatment option for BTP**

   KOL endorsement of FEBT will be critical to drive market anticipation for FEBT, stimulate product uptake at launch, and secure favorable reimbursement status. In addition, KOL/Pain Societies/Patient Advocacy Groups support will be crucial in efforts to secure a position for FEBT in BTP and chronic cancer and noncancer pain treatment guidelines.

7. **Minimize risk for abuse, addiction, and diversion**

   Like other CII drugs, there will be a fear of abuse, addiction, and diversion associated with FEBT. It will be important to minimize these risks by educating physicians regarding appropriate patient selection and monitoring. In addition, patients will need to be educated about the appropriate and safe use of FEBT for BTP.

Critical Success Factors/Strategies/Tactics

CSF#1 – Successfully convert ACTIQ loyalists to FEBT within the first 90-day period		
Marketing Objective	**Strategy**	**Tactics**
• Achieve high level of prelaunch awareness – >90% of ACTIQ 5-10 • Strengthen relationships with core ACTIQ prescribers by increasing call frequency among ACTIQ deciles 3-10 (baseline: 7.6 PDEs per decile 3-10 prescriber) (6 mths, 4/05-9/05) • Convert ACTIQ deciles 3-10 o 50% prescribed 1 time in first 3 mths o 50% of FEBT new patients maintain monthly Rx over 6 mths	**Prelaunch:** • Establish Cephalon as a committed partner and leader in the pain management community • Actively engage managed care and differentiate FEBT by providing a unique and attractive value proposition • Develop a strategic publications plan • Develop adequate, timely disease and product education awareness via appropriate vehicles • Deploy Pain Care sales force by 4Q '05 • Deploy MSLs 1Q '06 • Disseminate key FEBT clinical and scientific information • Establish physician loyalty initiatives to convert ACTIQ loyalists to FEBT adopters • Establish patient loyalty initiatives to convert ACTIQ patients • Build internal interdepartmental momentum **Launch:** • Establish a highly targeted launch plan to convert ACTIQ loyalists to FEBT adopters within the first 30- to 90-day period	**Prelaunch 2005:** • Conduct advisory boards to gain feedback on clinical and communication plan o PMEAB September 2005 o Consultants meetings 3Q-4Q '05 o Managed Care Advisory Boards 3Q & 4Q '05 • Conduct medical educational • Implement the Public Relations plan • Train the Pain Care sales force • Patient database development: Capture opt-in patient names to enable direct to patient communication o Web site: revise to include program to gather patient information and opt-in patients • ACTIQ 800#: Revise the 800# to include patient opt-in for future communication • ACTIQ Coupon Book: revise to include opt-in for patients **Prelaunch 2006:** • Continue opt-in initiatives initiated in 2005 • Launch the Pain Franchise campaign (see Tactical Overview section) • Conduct medical educational market conditioning programs • Scientific information booth at key pain associations meetings • Implement the Public Relations plan • Inform Managed Care of pending FEBT approval: conduct clinical discussions, create cost model, create the Dossier for the formulary review process • Implement clinical experience program by Q3 '06 • Prepare the Pain Care sales force for FEBT launch • Develop focused call plan to ensure sufficient reach and desired frequency

CSF#1 – Successfully convert ACTIQ loyalists to FEBT within the first 90-day period		
Marketing Objective	**Strategy**	**Tactics**
		• Coordinate MSL activities (KOL, MCO, Ad Boards, etc) • Publish the key clinical trials • Prepare the launch campaign materials • Alert wholesalers/pharmacies of pending launch via sell sheets and electronic communications • Conduct Consultant Meetings and MCO Ad Boards to gain feedback on refined clinical and communication plans • Develop Speaker Slide Kit and Speaker Training Program • Publish the noncancer clinical trials **Launch:** • Execute the distribution plan • Implement Publication Relations plan • Conduct the launch meeting • Disseminate the sales materials to the sales force • Execute the call plan strategy • Communicate to patients in the opt-in database • Coupon Program • Conduct Consultant Meetings and Ad Boards to gain feedback and to refine clinical and communication plans

CSF#2 – FEBT is clearly differentiated from ACTIQ and other BTP treatment options		
Marketing Objective	**Strategy**	**Tactics**
• Key clinical data are published prior to launch • Label supplement with 3039 data submitted to FDA immediately upon approval • Pain franchise campaign launched by 1Q '06 • OV delivery technology campaign launch by 2Q '06	• Differentiate FEBT from other treatment options, including ACTIQ, SAOs, and ROOs in development • Establish presence of OraVescent® delivery technology in pain market • Demonstrate a value proposition for FEBT by establishing and differentiating a new opioid class of ROOs from SAOs • Develop a strategic publications plan • Develop adequate, timely product education awareness via appropriate vehicles • Create ACTIQ prescriber and patient awareness of the pending approval of fentanyl in the OraVescent delivery technology • Negotiate optimal label which clearly differentiates FEBT • Establish physician loyalty initiatives to convert ACTIQ loyalists to FEBT adopters • Establish patient loyalty initiatives to convert ACTIQ patients	**Prelaunch 2005** • Implement medical education programs • Conduct advisory boards: physicians and managed care • Implement patient loyalty program • Develop Pain Franchise campaign; initial focus on corporate commitment to pain market transitioning into OraVescent science and technology • Create sales force and MSL communication materials to internally educate on the pain franchise and OraVescent delivery technology campaign • Create animated video describing the OraVescent technology; include animation in collateral materials (brochure, premium item, slide kit, direct mail) • FEBT development: brand identity, concepts, messages **Prelaunch 2006:** • Execute the Pain Franchise campaign-journal ad • Medical Affairs technology booth at medical meetings, direct mail postcards • Provide sales force & MSLs with information regarding pain franchise & OraVescent delivery technology campaign • Disseminate the OraVescent animation collateral materials • 3039 trial data are published by 2Q '06 • PK manuscripts published by 3Q '06 • Creation of launch campaign materials **Launch:** • BTP in noncancer trials published by 4Q '06 • Execute launch campaign materials • 3039 trial data included in sNDA to be submitted immediately postlaunch

CSF#3 – Sufficient resources are secured and aligned across internal departments		
Marketing Objective	**Strategy**	**Tactics**
• Clinical and Regulatory meet their milestones for NDA submission by September 2, 2005 • Critical studies published prior to launch • FEBT launch materials are approved and ready at launch • Sales force in place and prepared for launch	• Establish consensus among departments for optimal preparedness for FEBT launch • Ensure timely submissions (NDA & clinical pubs), Risk MAP development, promotional materials development, prelaunch marketing conditioning, and the sales force preparedness, etc	**Ongoing now through launch** • Conduct planning session meetings with appropriate staff to gain consensus and ensure alignment of resources • Create core FEBT interdepartmental teams: o PRC Team o Risk MAP o Labeling Committee o FEBT Planning Team o ISCP Team o Launch Team

CSF#4 – Physicians and patients have access to FEBT		
Marketing Objective	**Strategy**	**Tactics**
• By launch x% of TPPs are aware of FEBT (TBD with Bill Cunningham) • FEBT is placed on x% of commercial and noncommercial formularies within the first X months postapproval (TBD with Bill Cunningham) • FEBT is stocked by wholesalers by launch • Detail all identified FEBT stocking pharmacies within 6-month launch period	• Establish a comprehensive and coordinated managed markets plan • Develop a strategic publications plan • Demonstrate a value proposition for FEBT • Establish a new opioid class of rapid acting opioids (ROOs) and differentiate from SAOs • Develop a distribution plan to ensure FEBT is stocked at launch • Negotiate optimal Risk MAP: ○ Focus should be to minimize risk without compromising product growth in the appropriate patient population	**Prelaunch 2005** • Execute the Managed Markets plan initiatives (see Mgd Mkts Plan in Appendix 2) • Execute the tactical plan to support the adoption of a ROO class by USP, First DataBank • Initiate HEOR plan activities • Support dissemination of TJU guidelines **Prelaunch 2006:** • Execute the Managed Care Plan initiatives: inform managed care of pending approval, develop cost model, complete AMCP Dossier, develop slide kit, visual aids, etc • Continue execution of the HEOR initiatives • Execute the FEBT distribution plan initiatives • Actively engage managed care and differentiate FEBT by providing a unique and attractive value proposition via pain-dedicated trained speakers, MSLs, Marketing, and Managed Markets staff • Implement the tactic plan to support the establishment of the ROO class in USP and First DataBank • Trade Relations coordinates the implementation of a distribution plan to ensure FEBT is stocked at launch

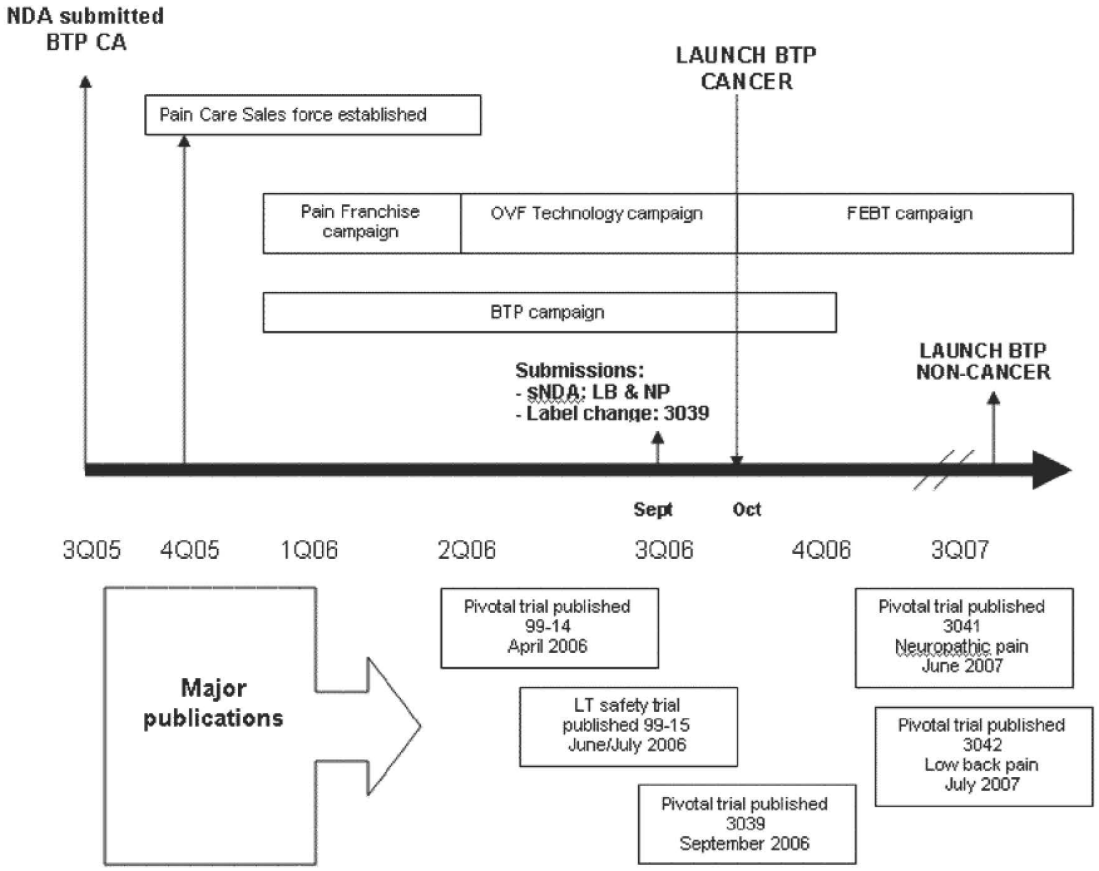
CSF#5 – Continue to develop BTP market by increasing awareness and understanding of BTP and its optimal treatment		
Marketing Objective	**Strategy**	**Tactics**
• Grow the ACTIQ/BTP TRx market (achieve ACTIQ TRx 2005/2006 objectives) • Achieve >50% awareness of ROO term by ACTIQ deciles 3-10	• Expand the BTP market by increasing physician and patient awareness of BTP – definition, characteristics, prevalence, appropriate diagnosis, assessment, and optimal treatment • Establish BTP as a clinical entity in chronic pain in need of treatment o Demonstrate the burden of illness of BTP o Demonstrate the suboptimal nature of current therapeutic options o Establish and differentiate a new opioid class of ROOs from SAOs for the treatment of BTP	**Prelaunch 2005** • Conduct retrospective studies (see HEOR Plan in Appendix 7) demonstrating the burden of BTP and the sub-optimal nature of current pharmacological options • Establish ROO term awareness o Meet with KOLs and conduct medical education initiatives to establish ROO term awareness o Incorporate ROO term in label and publications • Develop BTP awareness campaign materials – journal ad, slim-jim brochure, pain assessment tear sheets, direct mail campaign, BTP animation **Prelaunch 2006:** • Implement BTP campaign including 1-page BTP journal ad and booth presence • Direct mail campaign on BTP awareness and optimal treatment • Conduct a prospective clinical trial to create the value proposition of FEBT • Support dissemination of key BTP clinical information through medical education and publications • Provide sales force with the resources to strengthen relationships with core prescribers • Develop new chronic pain assessment tool with BTP component

CSF#6 - Key Opinion Leaders support FEBT as an effective treatment option for BTP		
Marketing Objective	**Strategy**	**Tactics**
• Obtain PMEAB and KOL endorsements of FEBT as valuable treatment option for BTP • KOLs recognize need to develop new chronic pain assessment tool with BTP component • KOLs recognize need to differentiate ROO from SAOs	• Enhance, expand, and leverage KOL relationships • Develop a KOL Strategic Plan • Deploy pain-dedicated MSLs by 1Q '06	**Ongoing now through launch** • Conduct the PMEAB meeting September 2005 • Involve PMEAB members in FEBT trials, publication of clinical data, and medical education initiatives • Involve KOLs in consultant/advisory meetings, FEBT clinical development, publications, validating BTP assessment & treatment guidelines, home office visits, medical education programs, etc • Establish Scientific information booth at key pain association meetings • Implement the PR Plan

CSF#7 - Minimize risk for abuse, addiction, and diversion		
Marketing Objective	**Strategy**	**Tactics**
• Achieve high awareness of FEBT RiskMAP objectives & resources within 6 mths postlaunch (>90% of deciles 3-10)	• Develop and implement a comprehensive Risk Minimization Program which meets FDA requirements as set by the standards in the recently issued FDA guidance document for developing Risk MAPs • Negotiate optimal Risk MAP to meet standards and minimum risk without compromising appropriate use and opportunity • Educate HCPs on appropriate patient selection (opioid-tolerant patients) • Educate patients about safe use of FEBT and allay fears of opioids • Support appropriate educational opportunities related to risk minimization	**Ongoing now through launch** • Issue grants to support educational efforts related to risk minimization (ESP) • Conduct physician and patient educational programs on risk minimization **Launch** • Implement Risk MAP initiatives

5 FEBT Marketing - Tactical Overview

Time Line of Key Activities/Milestones



5.1 Summary of Tasks

Condition the market (2005 through 2006):

- Enhance the Cephalon image as a partner committed to the pain community
- Enhance and expand relationships with KOLs
- Increase awareness and understanding of BTP and optimal treatment
- Demonstrate the burden of illness of BTP
- Establish and differentiate a new opioid class of Rapid Onset Opioids (ROOs)
- Prepare Managed Care/third party payers (TPPs) for the launch of FEBT

Prepare FEBT for launch (2005):

- Implement a clinical development program, including Health Econcomics Outcomes Research (HEOR), that supports launch of FEBT with a commercially competitive label for BTP in cancer by 3Q06 and an expanded label by 3Q07
- Continue Risk MAP development and negotiation with FDA

- Implement a communication plan strategy to differentiate FEBT and generate market anticipation
- Develop a value proposition for FEBT
- Determine branding elements, positioning and messaging; utilize these elements consistently even in the pre-launch phase
- Determine packaging
- Develop a pricing and negotiation strategy for Managed Care
- Establish and train the Pain Management Sales Force

Prepare FEBT for launch (2006 – up to launch)

- Continue to drive market anticipation for FEBT through appropriate vehicles (med-ed, pubs, PR)
- Continue to expand ACTIQ TRxs
- Implement a physician loyalty program
- Implement a patient loyalty program
- Implement internal communication initiatives
- Execute a Pain Franchise campaign to establish Cephalon as a committed partner and leader in pain market
- Execute the BTP campaign
- Execute an OraVescent technololgy campaign
- Continue to progress the clinical development program to support an expanded label
- Publish the BTP cancer
- Negotiate optimal BTP label and Risk MAP with FDA for BTP
- Finalize the pricing and negotiation strategy with MCOs
- Develop and implement the distribution strategy
- Prepare launch campaign
- Determine optimal targets and effective target approach
- Prepare Sales Force/MSLs/NAMs for launch
- Develop the call plan strategy
- Prepare for launch meeting
- Prepare 3039 Clinical Study Report for FDA submission as label change
- Prepare sNDA for low back and neuropathic BTP

Launch (3Q06)

- Launch FEBT:
    - Convert ACTIQ loyalists to FEBT adopters within the first 90 day period using a call plan that provides sufficient reach and a high level of frequency
    - Expand the physician prescriber base and drive new patient starts
- Submit 3039 label supplement to FDA immediately following approva
- Submit sNDA for non-cancer BTP immediately following approval
- Implement launch tactics
- Implement internal communications initiatives
- Implement a clinical experience program
- Publish the non-cancer clinical trials
- Assess message effectiveness, identify any barriers/objections and develop or adjust tactics if necessary

5.2 Promotional Budget Overview

The recommended promotional budget for Prelaunch and Launch activities for FEBT in 2006 is as follows: FEBT only expenditures – $13.6MM and FEBT + ACTIQ (both) expenditures – $12.6MM.

5.3 Promotion

5.31 Branding

1. Brand Identity Development

- **Description:** Based on the brand positioning and brand essence a series of fonts, logos, icons, and colors will be reviewed and selected to determine the final brand image
- **Project Objective:** Establish look and feel for the selected FEBT brand name
- **Implementation:** Final logo and colors will be incorporated into prelaunch and launch tactics
- **Timing:** Development May '05 to July '05

2. FEBT Concept Development

- **Description:** Concept will communicate the key FEBT messages and positioning through copy and art
- **Project Objectives:**
  - Develop a campaign that incorporates and relays the FEBT key messages and positioning
  - Increase awareness and drive prescribing for FEBT
- **Target Audiences:** Opioid-prescribing physicians, consultant physicians, and advisors
- **Implementation:**
  - Concepts will be tested at the 3 national consultants meetings and in field market research
  - Selected concept will be included in all prelaunch and launch branded initiatives
- **Timing:** Development May '05 to January '06; Implementation ongoing

FEBT Message Development

- **Description:** Based on clinical trial data, a series of key messages will be developed in the areas of BTP, efficacy, safety, bioavailability, dosing, patient preference, etc
- **Project Objectives:**
  - Determine the optimal product story components for launch and promotion of FEBT
  - Determine optimal ordering of messages

Target Audiences: Opioid-prescribing physicians, consultant physicians, and advisors

5.32 Patient Database

- **Description:** The purpose of this database is to capture both ACTIQ & cancer patient names, should it be decided that there is a need to communicate with them before/after the launch of FEBT. Names will be captured by making minor revisions to already existing materials
- **Project Objective:** Develop an opt-in patient database to collect contact information to enable direct-to-patient (DTP) communication
- **Target Audiences:** ACTIQ patients
- **Implementation:** Database will be developed and managed on an ongoing basis through Promotech
- **Timing:** Development July '05 to September '05; Population October '05 through launch

Patient Opt-In Mechanisms:

1. Web Site Revisions

- **Description:** Current ACTIQ Web site will be revised to include a program that will gather patient information and opt-in patients
- **Implementation:** Program will be developed and utilized up to launch and then incorporated into the FEBT Web site
- **Timing:** Development June '05 to September '05; Implementation October '05 to August '06

2. Revisions to Existing 800 #

- **Description:** Current ACTIQ 800 # will be revised so that when a patient calls in there is a way to have patients opt-in and collect contact information
- **Implementation:** This method can be developed and utilized up to launch. At that point, it can be switched over to an FEBT 800 #
- **Timing:** Development June '05 to September '05; Implementation October '05 to August '06

3. Coupon Book Revisions

- **Description:** Current Coupon Book will be revised to include 800 # so that patients can opt-in and information can be collected
- **Implementation:** Coupon books can be revised and used up to the launch of FEBT

Timing: Development June '05 to September '05; Implementation October '05 to August '06

5.33 BTP Communications Program

- **Description**: Concepts will be developed to raise disease awareness for BTP, as well as issues in treatment. Final execution will be educational – not promotional
- **Project Objectives:**

- Develop a cohesive campaign that incorporates and communicates BTP messages
- Build messages that can be incorporated into media and sales materials
- Increase awareness of BTP

- **Target Audiences:** Opioid-prescribing physicians and KOLs (investigators, consultants, advisors)
- **Implementation:** Concepts will be tested at the National Consultants Meetings in 3&4Q '05. Once finalized, the selected concept will be incorporated into
  - **Journal Ad** – 1-page ROB ad will discuss BTP and the issues in treatment, and placed into key pain journals (run March '06 through launch)
  - **Animation Video** – pain pathophysiology animation including intro to pain, neuro pathway, categorization (nociceptive vs neuropathic), acute vs chronic, BTP, and management issues
  - **Slim Jim** – 8- to 12-page brochure will incorporate the look/feel of the selected concept, as well as key information and images from the animated video
  - **Direct Mail:**
    - Mailer #1: Second-opinion mailer includes a customized envelope, cover letter, copy of the BTP slim jim, questionnaire designed to gain physician perceptions on BTP, and a BRC to obtain premium item (April '06)
    - Mailer #2: Mailer includes a small postcard and a copy of the BTP animation on a mini CD (May '06)
    - Mailer #3: Mailer includes a summary of the feedback on the questionnaire included in mailer #1 and a premium item, ie, medical textbook on pain (July '06)

Pain Assessment Tear Sheet – 2-sided tear sheet will be used to help patients to communicate their pain to physicians and help physicians assess their pain (July '05 through launch)

5.34 Franchise Campaign

- **Description:** Concepts will be developed to tell the franchise story: first corporate/pain commitment with a subsequent transition to a science/technology focus. Final execution will be educational – not promotional
- **Project Objective:** Create concepts that will best communicate the key franchise messages
- **Target Audiences:** Opioid-prescribing physicians, consultant physicians, and advisors
- **Implementation:**
  - Concepts will be tested with physicians at the last 3 national consultants meetings
  - Final concepts will be incorporated into campaign tactics
- **Timing:** Development July '05 to January '06

Franchise Campaign Tactical Executions:

1. Journal Advertising

- **Description:** 2 different set of ads will tell the franchise story:

  - The first will portray Cephalon's commitment to the pain market
  - The second will provide a graphic portrayal of the OraVescent delivery technology.
- **Implementation:**
  - Corporate/pain commitment: Ad will run first for 3 to 5 months
  - Scientific: Ad will run second for 3 to 5 months
  - Ads will run in key pain management journals, and, where applicable, will run simultaneously with a published journal article
- **Timing:** Development November '05 to January '06; Implementation March '06 through launch

2. Scientific Information/Technology Booth

- **Description:** A 20 x 20 booth incorporates the technology look and feel and provides a forum for Cephalon employees from the Medical Affairs and Clinical Departments
- **Implementation:** Booth will be displayed at all key pain conventions before/after the launch of FEBT starting with AAPM in February 2006
- **Timing:** Development June '05 to January '06; Implementation February '06 through launch

3. Booth Panels and Plasma Screen

- **Description:** Booth panels and plasma screens will provide visual focus for the technology story at key scientific meetings
- **Implementation:**
  - Placement and content of panels to be determined based on regulatory guidance
  - Panels and animation will run in the Scientific Information/Technology Booth
- **Timing:** Development November '05 to January '06; Implementation February '06 through launch

4. Direct Mail Postcards

- **Description:**
  - **Mailers #1 and #2:** Postcards include the look/feel and key messages from the corporate pain campaign concept
  - **Mailers #3 and #4:** Postcards include the look/feel and key messages from the OV delivery technology campaign concept
- **Implementation:**
  - Series of 4 mailers will be mailed from medical affairs over a course of 2 to 4 months during the prelaunch phase
- **Timing:** Development December '05 to February '06; Implementation March '06 to June '06

5. Sales Force Communication

- **Description:** Internal materials will be used to educate and inform Cephalon sales representatives on the franchise campaign and OraVescent delivery technology (with no mention of fentanyl)
  - Marketing update prelaunch teaser will provide reps with an overview of all franchise materials
  - During the course of the prelaunch phase, a sales force "theme" can be developed and implemented into sales meetings, direct mailers, incentive items, e-mails, voicemails, etc, in order to build anticipation for the product launch
- **Project Objectives:**
  - Inform the field on all of the franchise tactics
  - Build anticipation for the product launch
- **Target Audiences:** Cephalon sales representatives and MSLs
- **Implementation:** Distributed to all sales representatives and MSLs prior to the utilization of materials
- **Timing: Development November '05 to January '06; Implementation February '06 to August '06**

5.35 OV Technology Tactical Executions

1. Animation

- **Description:** Animated video will verbally and visually explain BTP, the OV delivery technology, and OraVescent story. Video will be developed in 3 segments, which will be implemented as allowed by regulatory guidelines and the expected timing of product launch. The first 2 segments (BTP and technology) will be implemented during the prelaunch phase in separate venues and then rolled out with the final segment (FEBT) at launch as 1 seamless video. Each segment will be about 2 to 3 minutes in length.
- **Project Objectives:**
  - Increase awareness for BTP (prelaunch)
  - Educate physicians on the OV delivery technology (prelaunch)
  - Build awareness and anticipation for the product launch
  - Build awareness for OraVescent Fentanyl at/postlaunch
- **Target Audiences:** Opioid-prescribing physicians, consultant physicians, and advisors
- **Implementation:**
  - Voice-over script and story boards will be shown and further developed at all 3 national consultants meetings
  - The rough animated video, including voice-over, will be submitted to a few key physicians for review and comments
  - In order to be flexible, final animated video will be compartmentalized to first roll out only the BTP and

technology portion of the story in the prelaunch phase and then roll out the whole story, including FEBT, after launch
    - **Segments 1-2:** Direct mail with CD, scientific meetings (plasma screens), speaker presentations, and Web; "snip its" may be used in journal advertising, booth panels, collateral, etc
    - **Segments 1-3:** Direct mail with CD, scientific meetings (plasma screens), speaker presentations, and Web; "snip its" may be used in journal advertising, booth panels, collateral, etc
- **Timing:** Development May '05 to January '06; Implementation February '06 through launch

2. Technology Brochure

- **Description:** 4-page brochure will incorporate the look/feel of the OV delivery technology campaign concepts, as well as the key messages and visuals from the animated video
- **Project Objectives:**
    - Prepare the market for the product launch
    - Educate physicians on the OraVescent delivery technology
    - Build awareness and anticipation for the product launch
- **Target Audiences:** Opioid-prescribing physicians, consultant physicians, and advisors
- **Implementation:**
    - The brochure can be used by all target audiences, and as a prelaunch educational piece for MSLs
    - Copies of the brochure can also be handed out in the booth or included in mailers
- **Timing:** Development November '05 to January '06; Implementation February '06 through launch

3. Premium Item

- **Description:** Premium item will be a "safe" tactic and correlate to one of the product's unique differentiating factors, ie, premium that displayed bubbles or demonstrated speed
- **Implementation:** Premium items can be distributed in multiple venues including booths at scientific meetings and direct mail campaigns
- **Timing:** Development October '05 to January '06; Implementation February '06 through launch

4. Mini Slide Kit

- **Description:** Small brochure and holder, 5 to 7 slides, and copy of the animation will tell the OraVescent delivery technology story
- **Project Objectives:**
    - Prepare the market for the product launch
    - Educate physicians and patients on the OraVescent delivery technology
    - Build awareness and anticipation for the product launch

- **Target Audiences:** Opioid-prescribing physicians, consultant physicians, and advisors
- **Implementation:**
  - Slide kit can be handed out at scientific meetings
  - Slides can be used in appropriate forums and as the FEBT Speakers' Bureau is assembled for training purposes
- **Timing:** Development November '05 to January '06; Implementation February '06 through launch

5. Top-Tier Direct Mail – Options #1 and #2

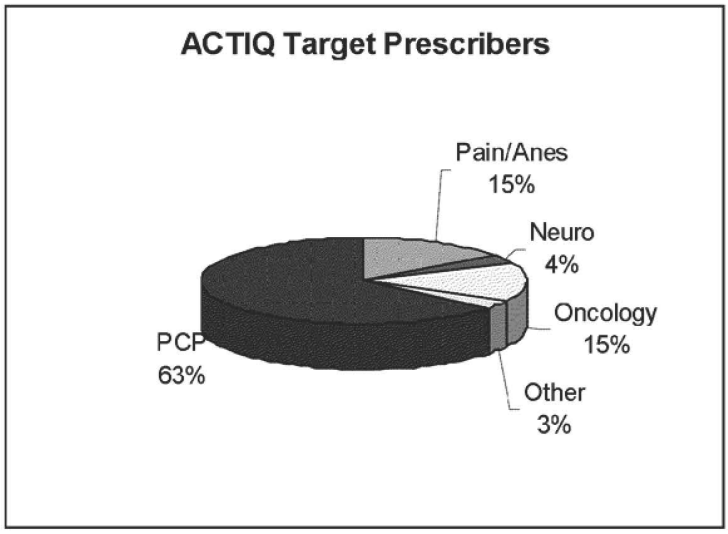
- **Option #1 Description:**
  - **Mailer #1:** Second-opinion mailer includes a customized envelope, cover letter, copy of the technology brochure, questionnaire designed to gain physician perceptions on the science, and a BRC to obtain premium item
  - **Mailer #2:** Mailer includes 1 of the postcards and a copy of the animation on a mini CD
  - **Mailer #3:** Mailer includes a summary of the feedback on the questionnaire included in mailer #1 and a premium item (this should be sent to all physicians regardless if they answered the questionnaire or not, in order to maximize awareness for the story during the prelaunch phase)
- **Option #2 Description:**
  - **Mailer #1:** Mailer includes a customized envelope; cover letter; stickers of headlines, subhead, and bullets options; blank journal ad with visuals only; and a return envelope
  - **Mailer #2:** Mailer includes 1 of the postcards and a copy of the animation on a mini CD
  - **Mailer #3:** Mailer includes a summary of the feedback on the journal ad included in mailer #1 and a premium item (this should be sent to all physicians regardless if they answered the questionnaire or not, in order to maximize awareness for the story during the prelaunch phase)
- **Project Objectives:**
  - Establish Cephalon as a leader in the pain category
  - Educate physicians on the OraVescent delivery technology
  - Build awareness and anticipation for the product launch
- **Target Audiences:** High-opioid prescribers and ACTIQ loyalist adapters
- **Implementation:**
  - Series of 3 mailers will be sent from Science Communication over a course of 2 to 4 months
- **Timing:**
  - **Mailer #1:** Development November '05 to January '06; Implementation February '06
  - **Mailer #2:** Development December '05 to February '06; Implementation March '06
  - **Mailer #3:** Development February '06 to April '06; Implementation May '06

5.36 Sales Force

Direct sales will be the cornerstone of the promotion strategy for FEBT. The Pain Care sales force consisting of 100 Sales Representatives and 12 Area Managers is slated to be in place by 4Q '05 to allow adequate time for the sales force to be trained, complete physician profiling, and establish relationships and rapport with their target healthcare providers.

5.37 Targeting

The total target physician list for FEBT will be based on a refined ACTIQ/SAO list. The list will include ~18,000 targets. Currently there are 30,259 ACTIQ physician targets who meet the definition of "knowledgeable and skilled in the use of opioids."



	Target #
Pain/Anes:	4485
Neurology:	1090

Source: SMART database Feb '04-Jan '05

The leading priority at launch will be to convert ACTIQ loyalists to FEBT adopters. There are a relatively small number of high-decile ACTIQ prescribers (~2500 accounting for 80+% of the TRx's). To drive this conversion a call plan will be established that has the appropriate level of reach and frequency to convert the key target ACTIQ loyalists to FEBT adopters within the first 90-day period postlaunch (see chart below for ACTIQ physician counts and additional potential physicians who write a large volume of SAOs).

ACTIQ Decile Summary Feb 2004- Jan 2005

Decile	ACTIQ Physician Count	LAO Physician Count	SAO* Physician Count	Pure SAO Physician Count	Combo SAO Physician Count
8-10	179	3330	20,725	2031	21,131
5-7	610	16,935	60,329	12,226	60,001

1-4	15,099	261,240	663,248	220,740	655,678
TOTAL	**15,888**	**281,505**	**744,302**	**234,997**	**736,810**
ACTIQ penetration		**6%**	**2%**	**7%**	**2%**

* SAO physician count includes pure and combo SAO.

As is evident in the table above, ACTIQ has penetrated only a small percentage of the pure SAO prescribers (7%). After the ACTIQ loyalists have been converted, the strategy for FEBT will be to expand the FEBT prescriber base by converting the non-ACTIQ, pure and combination SAO prescribers to FEBT users and adopters.

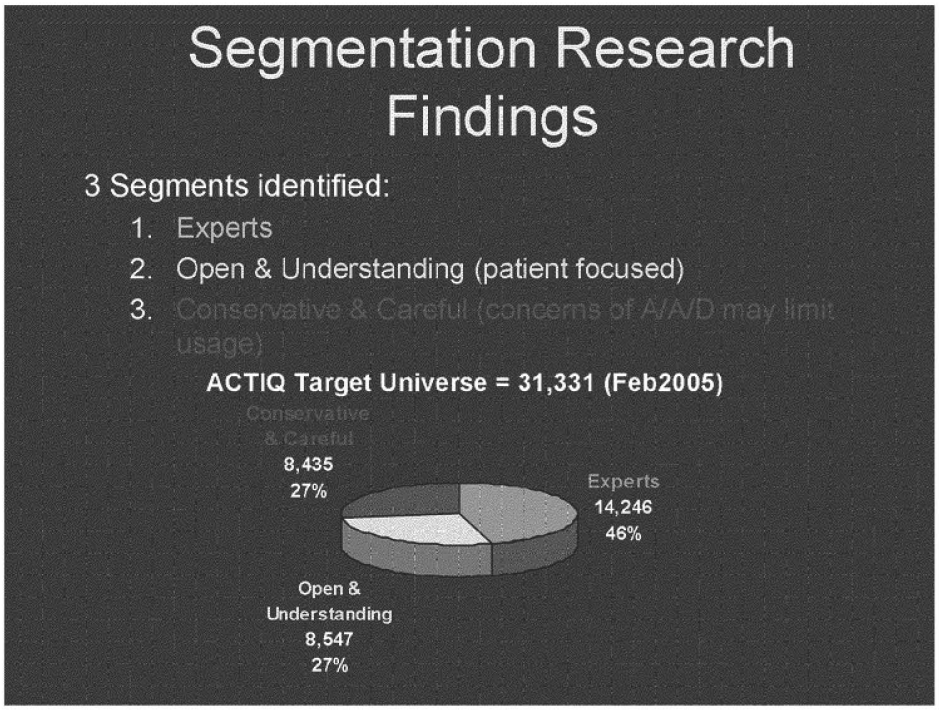
Physician Segmentation

In addition to establishing call priorities based on prescribing patterns, the brand team expects to provide the sales force with physician segmentation data that will provide additional insights into a physician's prescribing behavior and potiential. This additional insight into a physician's expertise/comfort with prescribing opioids may be used to set the sales call message strategy.

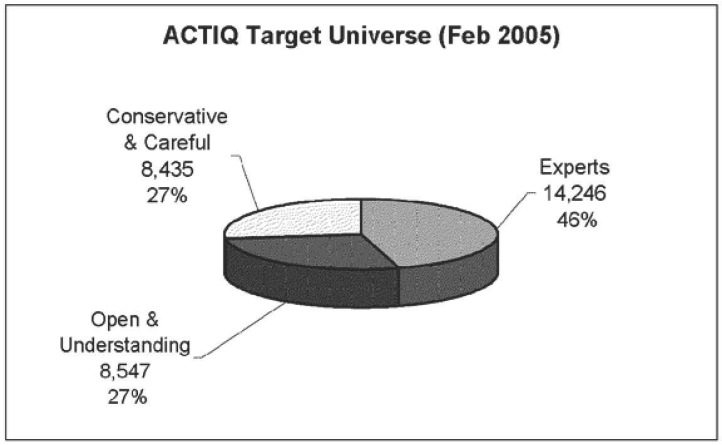
In the fall of 2004 market research initiated the segmentation project with the objective of refining the ACTIQ call targeting and messaging based on physician attitudes toward prescribing ACTIQ. The research identified 3 physician segments which are described in the table below:

Segment Name	Characteristics
Experts SAO Usage High TRx per Month >83* ACTIQ Potential: 1†	• Prefer to manage their own patients (rarely refer) because they consider themselves best equipped to handle severe pain • Favor "opioid agreements" • Comfortable using special procedures for pain management • Concerned about patients' opioid addiction/diversion, but has the patient management tools for dealing with these issues • Tend to not shy away from treating chronic patients long-term with opioids
Open and Understanding SAO Usage: Moderate TRx per Month <82* ACTIQ Potential: 2†	• Less sophisticated knowledge of pain management compared to experts but open to learning • More likely to refer severe chronic pain patients • Tend to be more patient centered and possibly more focused on quality of life (improved functioning) • Less likely to use special procedures
Conservative and Careful SAO Usage: Moderate TRx per Month <82* ACTIQ Potential: 3†	• Smaller portion of practice time focused on pain treatment • Concerns of abuse and diversion limit opioid prescribing • Least open to trying new pain medication • Tend to undertreat pain • Most likely to refer severe chronic pain patients • Less likely to use special procedures

Source: Primary Research Ziment Fall '04.



These segmentation profiles have been field tested in a small number of sales territories. Sales Force feedback indicated the segmentation data were useful in planning their sales calls in terms of messaging. The field test supported the hypothesis that the Experts and Open & Understanding targets were more receptive to ACTIQ compared to the Conservative and Careful physicians, though there were some individual physician exceptions. Conservative and Careful physicians typically treated less severe chronic pain compared to the other 2 segments and had more concerns regarding potential abuse and diversion of opioids. The chart below breaks down the number of ACTIQ targets by segment:



Source: Segmentation Study – Ziment Fall 2004

The next step is to provide the segmentation information to the Sales Force for use this year and to monitor its value over the coming time period. Feedback from the sales force

and additional research will be conducted to determine if this segmentation data will be applicable and of value to support the launch of FEBT.

Launch Call Strategy-TBD

		Months 1-3	Months 4-6	Months 7-12	Total PDEs
		2 PDEs/mth	1.5 PDEs	1 PDE	
ACTIQ prescribers by decile		26,172	19,629	26,172	71,973
Retail (3 per week?)					

For representation purposes. Actual call strategy to be developed with Sales Management.

5.38 Managed Markets

Securing favorable reimbursement for FEBT is critical; however, this objective must be weighed against the cost of securing favorable reimbursement. The Managed Markets Plan (see Appendix 2 for complete plan) outlines the tactics designed to identify the optimal strategic approach to achieving favorable reimbursement, the development of tools to support the strategies, and program implementation. The key aspects of the plan are listed below:

Part A: Determination of optimal strategy

1. Opportunity Assessment:
   - Advisory Board (5-7 attendees) meeting with former Managed Care executives to gain insights into the process for securing favorable reimbursement based on the projected market situation at launch (3Q '05)

.

2. Development of pricing and reimbursement model:
   - Designed to quantify pricing and reimbursement trade-offs developed in previous research
   - Provide input to FEBT forecast
   - Development timing – late 4Q '05

Part B: Customer Feedback

1. Customer Advisory Boards
   - Managed Care Advisory Board (10 attendees) to obtain customer insights into current pain treatment algorithms within managed markets, build customer relationships, and gain insights into their perceptions regarding the role of FEBT in their plans (October '05 at AMCP meeting)
   - Managed Care Advisory Boards (~10 attendees) to obtain customer insights regarding FEBT clinical and HEOR data, messages, contracting strategy, build customer relationships, and gain insights into potential impact of Medicaid Part D (1Q '06-3Q '06)

Part B: Tactics

- Establish pricing and contract strategy
- Leverage KOL/society/advocacy endorsements to gain favorable reimbursement status
- MSLs will support NAM efforts to navigate the Formulary Review process (Ongoing in 2006)
- Create Managed Care dossier
- Develop slide kit to support efforts to gain formulary approval/favorable reimbursement
- Develop materials to support BTP awareness initiatives with MCO customers
- Develop value-added tools
  - Utilize ESP components
  - BTP/FEBT educational materials
- Train and prepare NAMs for launch

Conventions

Conventions offer an important opportunity to interface with physician/customers and gain and exchange critical insights on the BTP market. In 2006 Cephalon will have a prelaunch educational presence (details TBD) at the following key meetings:

Name & 2006 date if known	Activity	Specialty/ Attendee #
AAHPM American Academy of Hospice & Palliative Medicine Feb 8-11 Nashville, TN	**ACTIQ** **Science Information Booth** - **BTP**	**Palliative Care** **500**
AAPM American Academy of Pain Medicine February 22-25 San Diego, CA	**ACTIQ** **Science Information Booth** - **BTP**	**Pain** **600**
APS American Pain Society May 2-3 San Antonio, TX	**ACTIQ** **Science Information Booth** - **BTP, OV Technology**	**Pain** **2000**
ASPMN American Society for Pain Mgmt Nurses March 31-April 2 Lake Buena Vista, FL	**ACTIQ** **Science Information Booth** - **BTP**	**Pain** **600**
AAN American Academy of Neurology April 1-8 San Diego, CA	**ACTIQ** **Science Information Booth** - **BTP** - **OV Technology**	**Neuro** **10,000**
ASAM American Society of Addiction Medicine May 4-7 San Diego, CA	**ACTIQ** **Science Information Booth** - **BTP** - **OV Technology**	**Psych** **800**
AMCP Academy of Managed Care Pharmacy April 5-8 Seattle, WA	**ACTIQ** **Science Information Booth** - **BTP** - **OV Technology**	**Pharmacists** **3000**
ONS Oncology Nursing Society May 4-7 New Orleans, LA	**ACTIQ** **Science Information Booth** - **BTP** - **OV Technology**	**Oncology** **8500**
ASCO American Society of Clinical Oncology May	**ACTIQ** **Science Information Booth** - **BTP** - **OV Technology**	**Oncology** **22,000**

5.310 Trade Relations/Distribution

In order to ensure FEBT is available at launch Trade Relations will notify wholesalers in sufficient time prior to launch. Promotional tools will be created to communicate the necessary information to support stocking initiatives.

At launch wholesalers and pharmacies will be notified via communications tools such as PharmAlert, Blast Faxes, etc.

5.4 Integrated Strategic Communication Plan

The Integrated Strategic Communication Plan is the overarching plan that outlines the message strategy, integrates the multiple components designed to communicate these messages clearly and consistently to Cephalon customers (see Appendix 9 for full ISCP Plan).

5.41 Publications

The FEBT publication plan includes the strategies and tactics for dissemination of FEBT clinical data. The goal is to publish the cancer BTP clinical data prior to, but no later than, launch for BTP in cancer patients. Subsequently, the noncancer BTP trial data will be published at best by 4Q '06, or at the latest by no later than 1Q '07. Publication of the trial data will be essential for securing reimbursement and promoting FEBT (see Appendix 3 FEBT Development Plan for detailed list of publications).

5.42 Key Opinion Leader Development

Third-party advocacy and medical education will be critically important to communicating core scientific messages and FEBT product messages when appropriate. Some of the key programs to carry these activities forward include the following:

- MCO & Pharmacy Director meetings to support the adoption of FEBT in Managed Care
- Symposia at key meetings utilizing key opinion leaders
- Inclusion of KOLs in the clinical development program
- KOL involvement in publications

5.43 Medical Education and Continuing Medical Education (CME)

Medical education will be conducted to increase awareness of BTP and its appropriate assessment, diagnosis, and treatment.

See the Pain Franchise Medical Education Plan for program specifics.

Major Initiative: Emerging Solutions in Pain (ESP)

Many clinicians have expressed a great need for assistance in the assessment of the risk of abuse, addiction, and diversion among the pain-patient population. *Emerging*

Solutions in Pain (ESP) is a branded educational initiative supported by Cephalon, Inc., in order to support the need for appropriate education in the field of pain management. *ESP* is an ongoing initiative that is being developed by physicians for physicians, pharmacists, and other healthcare professionals, to address some of the most critical issues in pain management today. Through the expertise of a cadre of leading pain and addiction medicine experts, the *ESP* program will provide clinicians with guidance in the implementation of good practice management techniques, emphasizing favorable interaction with regulatory and law enforcement agencies, as well as effective assessment, monitoring, and documentation strategies, which will contribute to the overall goal of optimizing outcomes for their pain patients.

5.44 Public Relations

Communicating directly with customers, both physicians and patients, provides numerous opportunities for increasing the visibility of FEBT and expanding the presence of Cephalon in the BTP market. Some of these opportunities include

- Publicize results of key clinical studies or analyses
- Highlight the output of key conferences, events, or symposia
- Publicize support for key patient advocacy groups
- Publicize presentations, abstracts, and posters at key medical meetings

5.5 Market Research

See the Pain Franchise Market Research Plan 2005/2006 (APPENDIX 10)

5.6 FEBT Clinical Development Plan

The following are the clinical trials being conducted to support the NDA for BTP in cancer patients:

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	LPLV	Claim
99-011 PK study	Healthy volunteers	FEBT 270, 810, 1080, 1300 mcg ACTIQ®1600	42	Establish the PK profile of FEBT	C_{max}, AUC, T_{max}	Completed	
99-018 Dose Proportionality	Healthy volunteers	FEBT 200, 500, 810, 1080 mcg	27	Determine if dose strengths proportional	C_{max}, AUC	Completed	There is dose proportionality among the dose strengths and multiples
1026-PK of multiple lower vs. higher dose	Healthy volunteers	FEBT 100 mcg, 400 mcg	24	4x100 mcg is equivalent to 1x400 mcg	C_{max}, AUC, T_{max}	2Q '05	Multiple lower dose strengths = to equivalent high-dose tab
1027-Dose proportionality	Healthy volunteers	FEBT 100, 200, 400, 800 mcg	24	Determine PK characteristics of doses and show proportionality	C_{max}, AUC	2Q '05	PK profile and dose proportionality

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	LPLV	Claim
1028-Absolute Bioavailability	Healthy volunteers	FEBT 800, ACTIQ®800, Fentanyl Inj, Fentanyl PO Sol.	24	Determine the absolute and relative bioavailability of fentanyl delivered via FEBT	AUC	2Q '05	ACTIQ to FEBT dosing recommendation
1029-MD PK	Healthy volunteers	FEBT 400 mcg	24	Determine the steady state kinetics of FEBT	C_{maxss} and C_{minss}	2Q '05	Steady state kinetics
099-14 Efficacy PIVOTAL TRIAL	BTP – Cancer	FEBT and PBO	120	Efficacy from 15-60 minutes, global evaluation of efficacy	SPID 0-30	1Q '05	Efficacy in BTP in cancer pts
099-15- OL 12-mo Safety	BTP – Cancer	None	400	Safety	Safety	2Q '06	Safety, exposure requirement
099-16 Safety	Cancer patients with mucositis	FEBT 200 mcg	18	Determine if PK of FEBT are altered in this population, tolerability	C_{max}, AUC, T_{max}	2Q '05	PK not altered in patients with mucositis
3039 Cancer BTP-Onset PIVOTAL TRIAL NOTE: Not in initial NDA—to be submitted for label change after approval	BTP – Cancer	FEBT vs placebo, crossover	70	Efficacy data from 5-120 minutes, time to meaningful pain relief	Switching data ACTIQ to FEBT	4Q '05	Differentiate FEBT

The following trials will support the sNDA for non-cancer BTP:

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	LPLV	Claim
3041 Efficacy PIVOTAL TRIAL	Noncancer BTP lower-back pain	FEBT and PBO	100	Efficacy from 5-120 minutes, onset of action, level of product preference	SPID 0-30	1Q '06	Efficacy in lower-back pain BTP
3040 OL Safety 12 mos	Noncancer BTP	None	600	Safety, QOL, physical & emotional functioning, ER visits, mood, sleep, BTP medication preference		3Q '06	Safety, differentiate FEBT, exposure requirement
3042 Noncancer BTP Neuropathic Pain PIVOTAL TRIAL	Noncancer BTP neuropathic pain	FEBT vs. placebo	100	Efficacy, time to meaningful pain relief, efficacy up to 120 min	Improved function and QOL, pt preference	1Q '06	Efficacy in neuropathic pain BTP

5.7 FEBT Health Economics Outcomes Research Plan

The following HEOR projects are planned to support efforts to secure favorable reimbursement:

Project	Objectives	Actions/Deliverables
Evidence-based review	Capture clinical, economic, competitive landscape	Action: Review the medical literature, clinical environment, and humanistic characteristics & and assess the medical literature on the economic burden of chronic pain and BTP among pain patients **Deliverable**: Provide input to the product team regarding HEOR issues to support product plan initiatives
Burden of Illness study examining **Work Productivity** among workers treated for chronic pain	Support for market access Create economic messages	Action: Conduct a retrospective database analysis in a worker population that will include manufacturing, transportation, telecommunications, and pharmaceutical workers to describe absenteeism, presenteesim, and medical service utilization **Deliverable**: Publication and data for Budget Impact Model
Economic Analysis of chronic and BTP among users and nonusers of ACTIQ	Product Differentiation Cost-effectiveness messages Support for reimbursement Support for market access	Action: Cost-effective analysis examining the impact of treating BTP and Pain flares in the right patients (ie, cancer, lower back pain, OA, sickle cell anemia) at the right time Action: Collect data from TJU Historical Prospective Study in patients with chronic and BTP, literature review, clinical trials 3040-3042, and Burden of Illness worker population study, Maine Medical Center **Deliverable**: Design a Budget Impact Model & Publication

Project	Objectives	Action/Deliverables
FEBT Dossier Update	Support reimbursement Support market access Tool for market support	Action: Work with internal departments and external vendors to develop FEBT dossier **Deliverable**: Design a budget impact model
Prevalidation and Validation of **Treatment Satisfaction** Questionnaire (PAIN Flare TSQ)	Product differentiation Develop value messages	Action: Conduct a prevalidation and cognitive debriefing for the development of the Treatment Satisfaction questionnaire in patients who experience pain flares (incl. BTP, pain crises, acute episodic pain, etc) **Deliverable**: Questionnaire
Validation of the Pain Flare TSQ	Product differentiation Develop value messages	Action: Validate the questionnaire in Phase IV clinical trials FEBT vs SAO, and FEBT vs LAOs **Deliverable**: Validation of the questionnaire & publications
EU Development initiatives	Support market access Product differentiation QOL & economic messages Support reimbursements	Action: Integrate HEOR into development plans and initiatives in order to assist in the reimbursement process in the EU

Project	Objectives	Action/Deliverables
Prevalidation of the **Acute Pain Episode questionnaire** and Prevalidation of Web site	Product Differentiation Develop value messages	Action: Develop a questionnaire to measure real time impact of BTP and the effect of immediate relief of pain and on levels of functioning in low back pain and neuropathic pain patients with BTP **Deliverable**: Cephalon-copyrighted questionnaire for use in future clinical trials and publications **Deliverable**: Successful use of PDA to capture BTP data and Web site design for physicians and patients to review data imputed close to the actual time of the pain crisis. The Web site would assist physicians in diagnosing and tracking pain crises. **Deliverable**: Questionnaire for future use in Phase IV trials.
Validation of the **Acute Pain Episode** questionnaire and Web site sesign	Product differentiation Develop value messages Strategy: Support and/or drive development of initiatives (ie, education, publications) to overcome prescriber and pt fears	Action: Validate the acute pain episode questionnaire in a Phase IV FEBT clinical trials **Deliverable**: Validated questionnaire, publication, poster presentation at major meeting

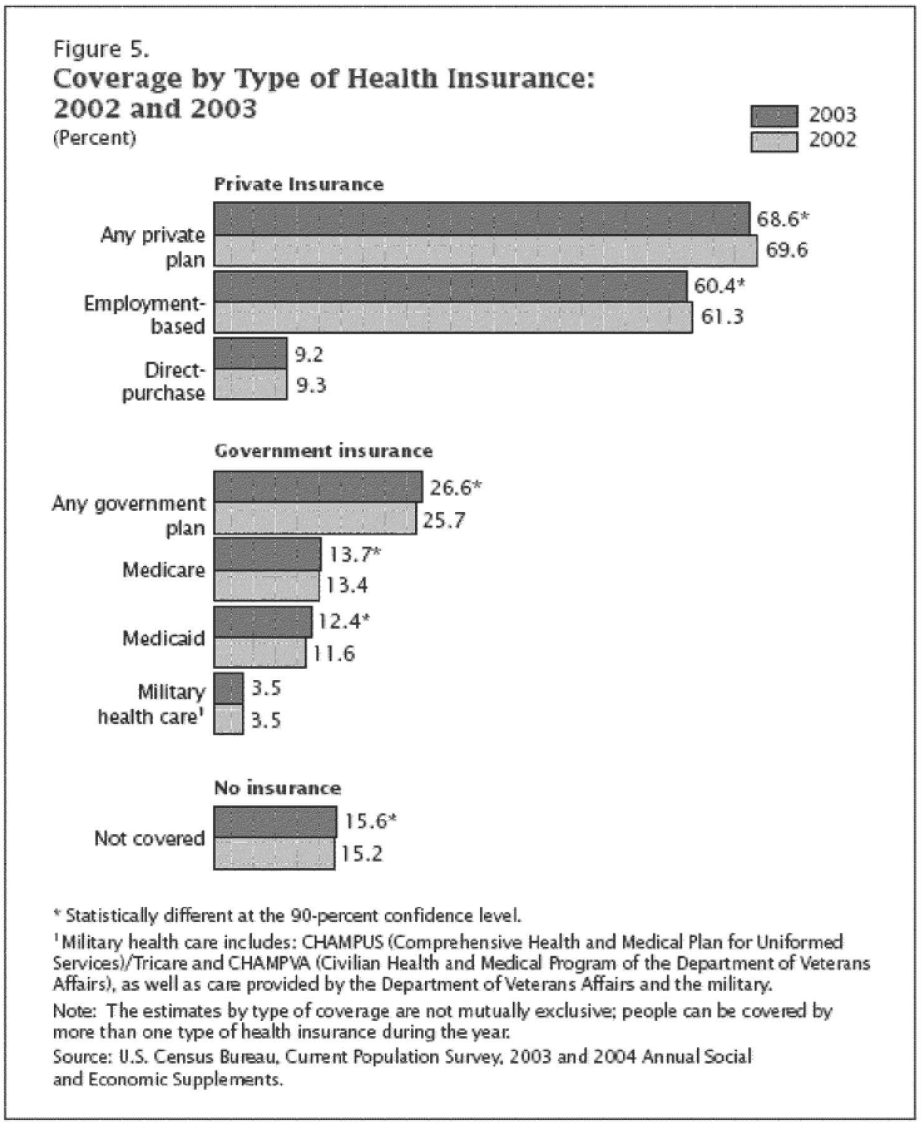
5.8 Launch Execution

A Launch Planning committee will be assembled by September '05 to plan for the launch of FEBT. In addition, a separate Launch Meeting Team will be assembled to execute the Sales Force Launch Meeting.

6 APPENDICES

Appendix 1 – Managed Care Background

According to the US Census Bureau in 2003, approximately 85% of Americans had some type of health insurance. The majority of these Americans have healthcare insurance via their employer (60%) or the government (27%). The amount of out-of-pocket expense to an individual/family for medical care and prescription drugs is highly variable depending on the structure of their healthcare insurance.

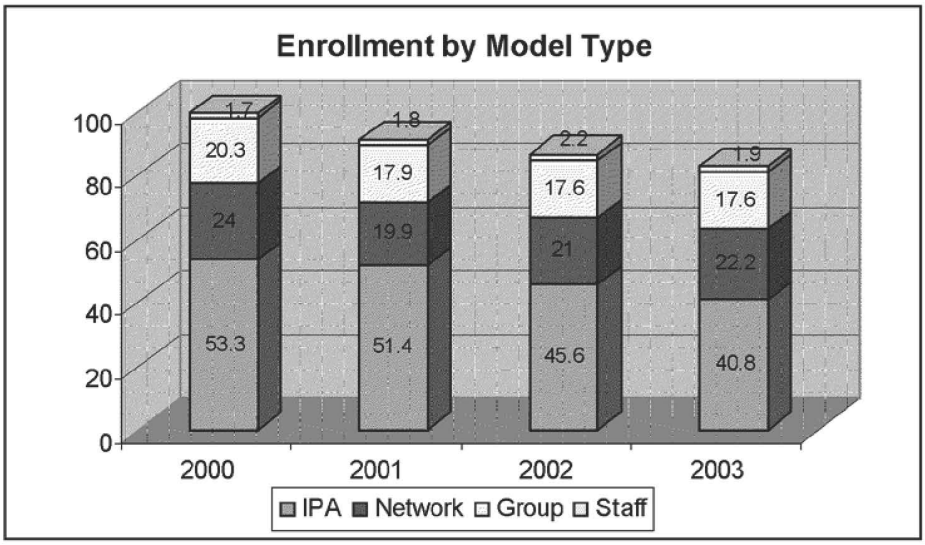


Indemnity insurance, the traditional fee for service healthcare, has become less prevalent as "managed care" has become the norm. This type of healthcare coverage is more expensive to the individual but offers the greatest flexibility of "choice" in terms of

healthcare services. Individuals pay a monthly premium plus are subject to a deductible that must be met before the health insurance company begins to contribute to an individual's healthcare costs. In addition, other forms of payments like co-payments per service or co-insurance (a certain percentage of healthcare costs) are fairly typical.

Managed care is an alternative to indemnity insurance. Managed care is a broad term and encompasses many different types of organizations, payment mechanisms, review mechanisms, and collaborations. These organizations are designed to ensure the provision of appropriate healthcare services in a cost-efficient manner. Systems and techniques used to control the use of healthcare services typically includes a review of medical necessity, incentives to use certain providers, incentives to use less expensive medications, and case management. Managed care has effectively formed a "go-between," brokerage, or third-party arrangement by existing as the gatekeeper between payers, providers, and patients.

According to Verispan LLC, the number of lives enrolled in managed care has been declining over the past 3 years, down from 99.3 million in 2000 to 82.5 million in 2003. This decline has been primarily in the IPA (Individual Practice Association) model. The numbers of enrolled lives by model type are displayed in the chart below:



Source: Verispan LLC 2004.

Model Type Definitions

Individual Practice Association (IPA) – An HMO model in which the HMO contracts with a physician organization that in turn contracts with individual physicians. The IPA physicians provide care to HMO members from their private offices and continue to see their fee-for-service patients.

Network Model HMO – A health plan that contracts with multiple physician groups to deliver healthcare to members. Generally limited to large single or multi-specialty groups. Distinguished from group model plans that contract with a single medical group, IPAs that contract through an intermediary, and direct contract model plans that contract with individual physicians in the community.

Group Practice – A group of persons licensed to practice medicine in the state, who, as their principal professional activity, and as a group responsibility, engage or undertake to engage in the coordinated practice of their profession primarily in 1 or more group practice facilities, and who (in their connection) share common overhead expenses (if and to the extent such expenses are paid by members of the group), medical and other records, and substantial portions of the equipment and the professional, technical, and administrative staffs.

Group Practice Without Walls – Similar to an independent practice association, this type of physician group represents a legal and formal entity where certain services are provided to each physician by the entity, and the physician continues to practice in his/her own facility. It can include marketing, billing and collection, staffing, management, and the like.

Staff Model HMO – A model in which the HMO hires its own physicians. Very much like the group model, except the doctors are employees of the HMO. Generally, all ambulatory health services are provided under 1 roof in the staff model.

Government Beneficiaries

The total number of government beneficiaries enrolled in HMOs rose 4.3% in 2003 to 21.1 million from 20.2 million in 2002. The numbers of 2003 enrolled government beneficiaries by model type are listed in the table below:

2003 Government Beneficiaries Enrolled in HMO by Type (000)

	Medicare Risk	Medicare Cost	Medicaid	FEHBP (Federal Employee Health Benefit Plan)	Total HMO Govt.
IPS	1593	115	6403	1242	9354
Network	1804	137	4881	534	7356
Group	1291	116	1600	516	3523
Staff	121	26	581	106	834
Total US	**4809**	**394**	**13,465**	**2398**	**21,066**

Source: Verispan LLC 2004.

Managed Care Types

Currently many managed care plans offer different types of plans:

- Preferred Provider Organization (PPO) – very common
- Point-of-Service (POS) – not very common
- Health Maintenance Organization (HMO) – the original form

The basic characteristics of all 3 are the same; they are designed to encourage the individual to seek care within the network. The difference is mainly in the degree of compensation for medical treatment outside of the network.

As of 2003, Verispan noted that 100% of the tracked managed care plans adhered to drug formularies. Most plans review their formulary on a quarterly basis (56%) while some (19%) review the formulary on an annual basis. Only a small percentage of plans review their formulary on a monthly (6%) or semi-monthly basis (8%).

The majority of plans have a 3-tier co-pay system while a limited number (7%) of plans do have a 4-tier system. Slightly greater than 90% of plans have no cap on the drug benefit. In the plans (approximately only 9% of plans) that do implement individual drug benefit caps, the annual average is $2500.

In 2003, 82% of managed care plans required substitution of generic drugs when they were available. There is an increasing trend for plans to require members pay a higher co-pay for the branded product if they refuse a generic alternative (72% of plans in 2003), or pay the difference between branded and generic cost (60% of plans), or even to pay the entire cost of the drug (19% of plans).

In addition to co-pay tiered systems aimed at patients, managed care also tries to influence physician-prescribing behaviors. These techniques are listed in the table below:

	No controls	Financial incentives	Drug utilization review (DUR)	Quality assurance	Second opinion	Prior authorization	Step edits	Practice guidelines
IPS	0.4%	31%	93%	76%	4%	92%	76%	80%
Network	0.0%	21%	82%	55%	1%	93%	72%	65%
Group	0.0%	30%	85%	75%	3%	95%	92%	80%
Staff	0.0%	21%	71%	79%	14%	93%	79%	71%
Overall Average	**0.2%**	**28%**	**88%**	**69%**	**4%**	**93%**	**77%**	**75%**

Source: Verispan LLC 2004.

The majority of managed care plans, regardless of type, use Pharmacy Benefit Managers (PBMs) to handle prescription services. Most plans utilize PBMs to manage prescription claims (90%), perform DUR (69%), other administrative services (67%), and/or dispensing (58%).

Medicare

Medicare is a federal health insurance program for people age 65 and older and for individuals with disabilities. The Medicare benefit is administered and funded in 4 parts:

Part A covers:

- Hospital care, nursing home, home health, and hospice.
  - No monthly premium for this coverage.
  - Cost sharing via co-pays and deductibles for hospital care.
  - Pharmaceuticals used in the hospital are covered.
- Inpatient hospital care accounts for 40% of all spending in Medicare.

Part B covers:

- Any person eligible for part A is eligible for part B.
  - Monthly premium of $66.60/month required.
  - Covers physician visits and clinical lab services.
  - Hospital outpatient and ambulatory surgical services.

- Pharmaceuticals administered by physicians in office or outpatient setting.
- Rx administered in physician office are covered by Medicare (certain injectibles, etc). Self-administered Rx are paid for by recipient.

Part C covers:

- Medicare + Choice
  - Managed Medicare paid by capitation system.
  - Provides more choices for beneficiaries.
  - 79% of beneficiaries have access to these types of plans but only 11% have enrolled.
  - Typically a generic-only formulary.

Part D: a new outpatient drug-benefit option

In 2003, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) was enacted into law. The MMA establishes a new voluntary outpatient prescription drug–benefit program. This new benefit becomes available to beneficiaries beginning on January 1, 2006.

There are 3 ways a beneficiary may have Part D coverage:

1. "Medicare Advantage," like part C, a managed Medicare plan with medical and pharmacy benefits. The plan has the risk.
2. "Prescription Drug Plan," or PDP. Member stays in Medicare FFS for medical benefit but signs up with a PDP, most likely a PBM for drug benefit. PBM has risk for drug spend.
3. "Fallback Plan" – in any area where there is not at least 2 private plan options, it becomes Medicare's responsibility or risk to cover pharmaceuticals.

The benefit will be administered by PBMs and Managed Care. The Part D drug benefit generally includes all drugs covered by Medicaid and excludes all drugs for which payment is made available under Medicare Parts A and B. However, the MMA permits plans to use formularies provided they meet certain standards. Plans are required to include in their formularies drugs within each therapeutic category and class. A model classification system is being developed by the United States Pharmacopeia (USP). The USP has established a Model Guidelines Expert Committee to develop the model.

- The USP has created an initial draft of Model Guidelines consisting of therapeutic categories and associated pharmacologic classes—work is ongoing.
- USP is also charged with revising the classification periodically to reflect changes in therapeutic use of covered drugs and additions of new covered drugs.
- The Centers for Medicare and Medicaid Services (CMS) is charged with overseeing the implementation of the drug benefit to ensure the formulary does not substantially discourage enrollment by beneficiaries.
- Plan Sponsors are not required by law to use the USP model guidelines; however, it appears they are being encouraged to do so.

Plans will have flexibility (subject to certain constraints) to establish varying features of the formulary:

- Levels of cost-sharing requirements and coverage limits other than "standard" coverage
- Lists of drugs to include on their formulary, and on which tier
- Cost management tools, ie, PA, step therapy, tier levels

The Medicare Part D benefit program specifics continue to evolve. Cephalon will monitor program developments and adjust strategies accordingly. For additional information see Appendix 8 for a Medicare Part D presentation prepared by the Cephalon National Accounts Team.

Appendix 2 – Managed Markets Plan

MANAGED MARKETS SITUATION

BTP Is Not Well Understood by Clinicians or Health Plan Decision Makers

The definition of breakthrough pain (BTP) is imprecise in that it broadly describes 3 quite different types of pain:

- **Incidence pain**—associated with a specific activity, but is unpredictable because for some patients pain does not occur consistently with the activity, while for others the activity that triggers the pain occurs unpredictably
- **Episodic pain**—the purest form of BTP, episodic pain also occurs unpredictably and is not associated with loss of analgesia or a physical activity
- **End of dose pain**—the reemergence of chronic pain due to the diminishing effect of an LAO.

Because end-of-dose pain is included in the broad definition of BTP, it dilutes the importance of a key characteristic of BTP that makes it both a personal challenge for the sufferer and a clinical management challenge for the clinician. That characteristic is "unpredictability." End-of-dose pain simply occurs in response to inadequate dosing of the LAO, a problem that can be resolved easily and inexpensively by adjusting dose or frequency of the LAO.

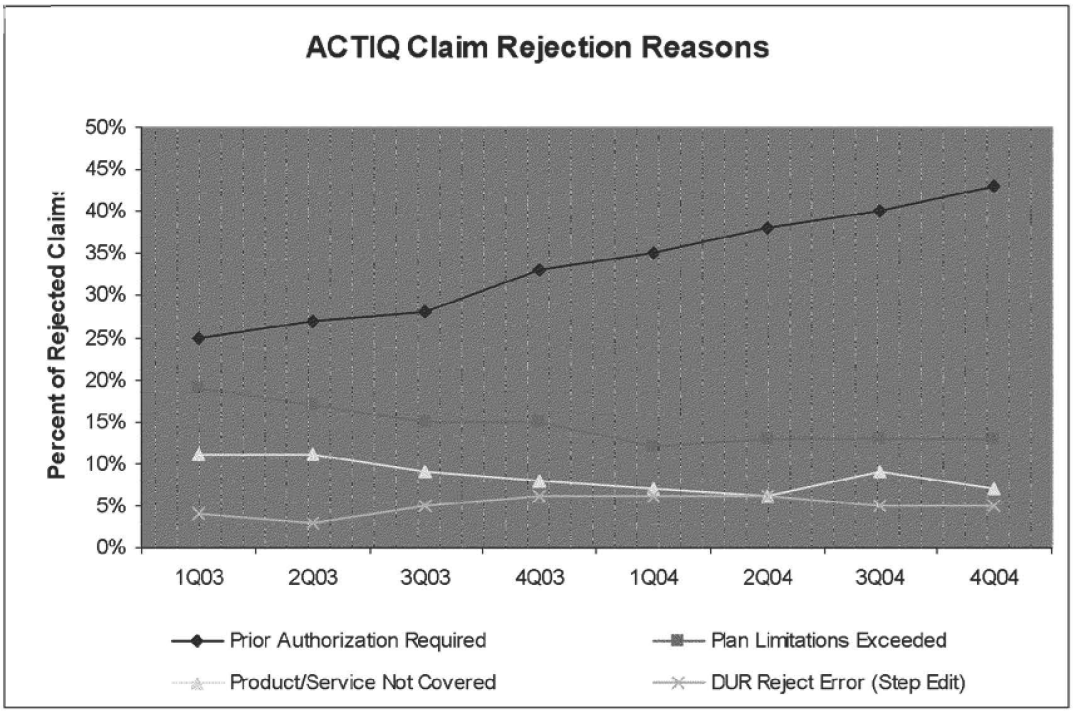
Current Treatment Patterns for BTP Suggest SAOs Are Adequate for BTP

Although a 2-part consensus recommendation on the assessment and management of BTP was just published in the journal *P&T*, no single authoritative algorithm guides the treatment of BTP. Currently, clinicians rely on LAOs and pure or combination SAOs to manage BTP, choosing from a wide variety of low-cost generic and branded products. The decision tree for the treatment of BTP was elucidated in market research conducted among medium-to-heavy ACTIQ prescribers (see chart below). ACTIQ was included within the SAO branch but separated on its own limb, most likely in recognition of its unique pharmacologic profile, dosing form, and cost. Nevertheless, this research suggests that ACTIQ and SAOs are considered clinically interchangeable by prescribers.

Thus while ACTIQ, the archetypal ROO, is recognized as different, that difference is not fully appreciated for its clinical importance. Essentially, the prevailing attitude among prescribers might be summed up as, "ACTIQ is a high-performance, luxury SAO."

Managed Care Organizations (MCOs) Are Increasing Restrictions on Expensive Medications

Despite significant hurdles to access erected by managed care plans, claim approvals for ACTIQ held steady at ~94% through 2004. As impressive and encouraging as this performance is, without further primary research it is impossible for us to quantify the impact that prior authorization has had on ACTIQ prescribing. Physicians committed to the idea of an ROO will take the steps necessary to ensure that their patients with BTP get ACTIQ. Our data, however, shed no light on the behaviors of less committed prescribers.



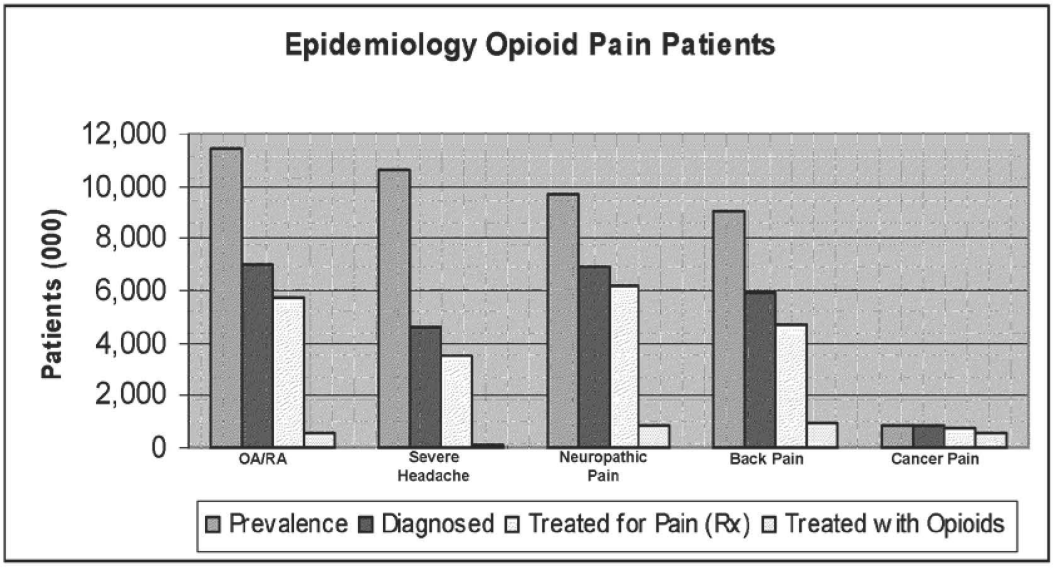
Furthermore, FEBT will launch into a market where generic fentanyl lozenges (OTFC) will be available from Barr Pharmaceuticals. Even if a managed care plan authorizes the use of an ROO, they will most likely give generic OTFC the most favorable reimbursement status because of lower price and perceived parity. Therefore, Cephalon must assess the effects of downward pressure on pricing on the volume of ROO category sales and whether less-than-premium pricing creates an opportunity for FEBT to dominate the category. It will be critical that FEBT be differentiated from OTFC in order to command some level of premium pricing vs generic OTFC. Marketing must determine which of the possible scenarios has the greatest commercial viability for Cephalon: lower price plus high share of a growing new segment (ROOs), or higher price in an increasingly competitive and restricted market.

Strengths	Weaknesses
• Cephalon's high BTP market IQ • Experienced National Accounts team • Rapid-onset analgesia of FEBT • More convenient to use formulation compared to ACTIQ • Growing relationships with key opinion leaders (KOLs) • MSLs will help expand KOL relationship to provide valuable scientific communications to pain specialists • Support of Emerging Solutions in Pain (ESP) program	• Limited ability to differentiate from ACTIQ and generic OTFC without clinical trial data from 3039 in the label • Label limited at launch to BTP in cancer • Inherent abuse potential of opioids (CII) • No HEOR benefit analysis • No QoL data • Assumed premium price
Opportunities	**Threats**
• Increase awareness of BTP, its proper assessment, and appropriate treatment (ROOs) • Establish ROO as a new and distinct category within United States Pharmacopoeia (USP) classification system • Demonstrate value proposition for ROOs and FEBT for patients with BTP (work, family, physical activities): • Clinical evidence showing superiority of ROO vs SAO for treating BTP • Establish and take leadership position with respect to ROOs • Managed markets contracting for less restrictive hurdles for reimbursement	• Generic OTFC • Third-Party Payers' (TPP) limited understanding of BTP and its appropriate treatment • Growing reimbursement restrictions • Counter-details from plans (PharmD) • Counter-detailing from competition • KOL perception that SAOs and ROOs may reinforce aberrant behavior • Increased regulatory scrutiny of and media focus on the opioid class • Future branded competition

KEY MANAGED MARKETS ISSUES

1. Low awareness and limited understanding of appropriate diagnosis, assessment, and appropriate treatment for BTP by third-party payers (TPPs)

Despite the commercial success of ACTIQ to date, many patients suffering from BTP are inadequately managed with SAOs. This is because many physicians, including pain specialists and oncologists, are unaware or do not have a full appreciation of the nature, incidence, and impact of BTP and the need for ROO. The table below presents derived estimates of prevalence, diagnosis rates, and treated patients by the leading disease states treated with opioids:



Source: Analysis of secondary data reports by Cephalon Market Research Department.

2. Absence of time to convert ACTIQ loyalists to FEBT adopters

The most significant marketing issue facing Cephalon with FEBT™ stems from the agreement with the FTC allowing Barr Laboratories to market generic OTFC upon final approval (and ACTIQ patent expiration September 2006—it's not just the Barr situation) of FEBT and compelling Cephalon to assist Barr if they are incapable of manufacturing OTFC. This leaves Cephalon little time to establish FEBT as the ideal therapeutic (unsubstitutable) option for BTP.

Barr is expected to launch their generic OTFC at least 30 days prior to the introduction of FEBT. Retail pharmacies will update their systems for a generic OTFC alternative as soon as it becomes available. Most health plans have mandatory generic substitution policies and therefore the majority of new ACTIQ prescriptions will be substituted. In addition, in an effort to control costs health plans may establish prior authorization and/or step edits to limit FEBT usage.

Furthermore, prescriptions for CII products may not be refilled. Patients must see their prescribing physician on a monthly basis to receive their next CII prescriptions. As a result of this, there is a limited window of opportunity to convert ACTIQ loyalists to FEBT before generic OTFC becomes firmly entrenched in the market.

The successful proven industry practice has been to drive product switches to the successor brand prior to the introduction of a generic alternative, optimally 12 to 18 months prior to loss of exclusivity. A successful conversion within managed care largely depends on the following variables:

- Adequate time to establish provider and patient demand and preference for the successor over the precursor
- A clear and meaningful differentiation between the precursor and its successor, which supports either cost-neutrality or cost-effectiveness (eg, greater clinical benefits for identifiable patients, proven reduction in other healthcare costs, favorable pricing or a combination of all 3). Therefore, beginning as soon as possible, Cephalon must establish FEBT as the superior ROO based on the following clinical profile:
  - Rapid onset of analgesia
  - Effervescent, quick-dissolving tablet formulation (no stick)
  - More consistent and predictable delivery of fentanyl than other formulations
- Sophisticated and well-trained managed markets national account team that can engage in a productive dialogue with managed care decision makers
- Comprehensive and flexible managed markets strategy to optimize reimbursement (reimbursement that lowers barriers to patient access to FEBT) or to overcome health plan resistance (eg, prior authorization, etc)

Ultimately, a lack of switch time, the immediate availability of generic OVTF, and the proven efficiency with which managed care organizations switch patients to generic substitutes supports the assumption that ACTIQ brand sales will erode at a rapid rate. This makes the time period prior to launch and immediately following the FEBT launch (30-90 days) critical to the success of FEBT.

Prior to launch it is imperative to secure sufficient resources to establish the clinical potential of FEBT through health economic and phase IV clinical trials that will prove its value in specific patients and grow its potential utility beyond those patients currently treated with SAOs, ACTIQ, or OVTF.

It will also be critical for Cephalon to develop a 2-part contingency strategy that optimizes the commercial value of FEBT. The first option will be to *appropriately* trade price (via rebates, discounts, etc) for lower barriers to usage and better reimbursement. The second option will be to support physicians and patients in optimizing reimbursement and overcoming barriers, such as prior authorization.

3. Limited KOL relationships to influence treatment algorithms and MCO policy

Cephalon has limited relationships with KOLs compared to other companies that market branded pain medications. Favorable expert opinion supporting the appropriate use of FEBT will help encourage MCOs to lessen expected restrictions to access for patients with BTP.

Cephalon must expand and solidify these important relationships and engage these KOLs in market conditioning activities in anticipation of the launch of FEBT. They will be required to interpret, and disseminate the recent consensus panel recommendations published by Bennett, Burton, and Fishman, et al, in the June 2005 issue of *P&T*. These should become the foundation of more official, sanctioned guidelines for the use of ROOs in the treatment of BTP and for differentiating FEBT from OTFCs. These guidelines can provide compelling evidence to support a unique place for FEBT on the drug formularies of managed care plans, Medicaid, and Medicare.

4. Significant resources required to create demand and pull through

Demand will be a major determinant of MCO interest in covering FEBT. This demand must come first and foremost from pain specialists, who are the highest prescribers of opioids. At a grassroots level, the expert opinion of practicing pain specialists will weigh heavily, especially if they're willing to write letters of medical necessity to assist patients who they believe benefit most from FEBT.

In order to effectively mobilize these important customers Cephalon will need to allocate significant budgetary and personnel resources for FEBT prelaunch and launch activities, which include but are not limited to the following:

- Clinical development opportunities for Phase IIIb & IV studies (including HEOR)
- Market conditioning to establish a new, emerging class of opioids (Rapid Onset Opioids—ROOs) and differentiate FEBT from OTFC
- Key Opinion Leader activities such as clinical research, medical education around BTP assessment and treatment

In light of the fact that resources are limited and Cephalon will be engaged in the launch of other new brands around the same time as the anticipated introduction of FEBT, a clear assessment of priorities and return on investment must be made for all marketing activities. These investments must be evaluated with the realization that Cephalon may be required to sell FEBT below the cost of ACTIQ in order to create access to FEBT for all appropriate patients who suffer with BTP.

5. Anticipated restrictive reimbursement status

The experience to date with ACTIQ plus the addition of generic OTFC to the market make it a virtual certainty that MCOs will continue to prefer SAOs for first-line treatment of BTP, reserving OTFC for more difficult clinical situations. TPPs are expected to continue driving business to generics when available and placing restrictions on premium-priced products, unless HECON analysis reveals compelling benefits to justify the price. Since the clinical performance of ACTIQ (or generic

OTFC) will compare closely with that of FEBT, aggressive pricing may be required to achieve "compelling benefits." (It is anticipated that FEBT will be premium priced.)

Status of TPP reimbursement of FEBT will have an impact on the success of the brand. TPPs will limit access to FEBT by the following mechanisms: prior authorization, usage/quantity limits, step treatment requirements, and tiered co-pay structures. The development of a comprehensive managed care plan must be completed well in advance of the launch to minimize these potential barriers and support the access of FEBT for appropriate patients.

6. Limited ability to clinically differentiate FEBT from generic OTFC

At launch the FEBT label will be based on 1 pivotal clinical efficacy trial, the 99-14 trial. The primary end point of this trial was pain relief beginning at 15 minutes postdosing. This trial design is identical to the ACTIQ pivotal trials. Cephalon is conducting a second clinical efficacy trial in cancer patients with BTP. This trial (3039) is designed to differentiate FEBT from its competitors based on its speed of onset. This study measures onset of pain relief as early as 5 minutes and time to meaningful pain relief as measured by stopwatch. This trial will not be completed in time to be included in the initial FEBT NDA. It will be submitted in a sNDA immediately upon product approval. Data from this trial are expected to be published by launch. While these data will be in the public domain, they will not be in the FEBT label, thus their utility to Cephalon to support FEBT differentiation will be limited.

COMMERCIAL VISION FOR MANAGED MARKETS

Establish FEBT as the preferred treatment for BTP in appropriate patients, as follows:

Short-term (Market Conditioning)

- Improve TPP's understanding of BTP and its appropriate treatment (including the burden of illness: personal, societal, and economic impact)
- Build the foundation for a new treatment algorithm that identifies ROOs as preferred treatment for BTP
- Assist MCOs in understanding the appropriate patient population for FEBT treatment within their plan
- Differentiate FEBT based on its unique delivery platform and combination of patient benefits (eg, rapid onset of analgesia, predictability, and ease of use)
- Build rapport with key managed care decision makers

Middle-term (Year 1)

- Gain favorable reimbursement status for FEBT status as the preferred ROO to facilitate switching patients from ACTIQ and driving new patient starts

Long-term (Year 2 and Beyond)

- Maintain and expand the number of plans who have favorable reimbursement status for FEBT
- Maintain leadership share of ROO class in face of new product introductions
- Solidify FEBT as the optimal choice for treatment of BTP
- Evolve toward market expansion into nonmalignant pain

CRITICAL SUCCESS FACTORS FOR MANAGED MARKETS

Authoritative treatment guidelines are available that support proper assessment, diagnosis, and appropriate treatment of BTP and recommend ROO as preferred treatment

The treatment guidelines for BTP should be issued by consensus opinion from leading pain management experts. They must inextricably link the clinical challenges of BTP with the benefits of FEBT (rapid onset, predictable absorption, and discrete dosing form [no stick]) and assist practicing pain specialists in identifying appropriate patients for FEBT. Guidelines for proper use would help MCOs establish objective criteria for assessing the medical necessity for use of FEBT and help them to direct prescribers in proper patient selection, focusing on those patients for whom the clinical benefits of FEBT are unmatched by a less expensive alternative.

Comprehensive HECON support for treatment of BTP with ROO

Compelling evidence must support the recommendation to use ROOs, and FEBT specifically, for the optimal treatment of BTP. This evidence should include the following:

- Estimates, backed by clinical research and data analysis, comparing the economic burden of BTP against the potential impact of the proper management of BTP
- Quality of life data showing FEBT help people with BTP reengage in family, recreational, and business activities. While these QOL outcomes will be needed and tell the humanistic side of the story, alone they will not motivate managed to care to grant favorable reimbursement status

Addressing this critical success factor will require that Cephalon first develop and disseminate data supporting the fact that the burden of illness associated with BTP is large and current treatment practices (overreliance on SAOs) contribute to the problem. Cephalon must also demonstrate that FEBT can reduce the personal, societal, and economic burdens of BTP.

Additionally, providing proper treatment for patients with documented BTP is not a "cost driver" in the healthcare system and on an individual basis pales in comparison to the benefits.

Establish the Rapid Onset Opioid (ROO) class for the treatment of BTP

The clinical profile of ACTIQ, OTFC, and FEBT is vastly different from the SAO class. Establishing the pharmacologic uniqueness and clinical utility of this new class is essential to differentiating the transmucosal fentanyls from SAOs and owning the BTP component within chronic pain management. This will also be an essential step in creating a new drug class within the USP classification system.

FEBT value proposition (outcomes + price + contracts) lowers barriers to access and encourages reimbursement

Ideally, clinical and health economic data for FEBT should show that it delivers a highly desirable clinical outcome, which can be optimized through proper patient selection and implementation of treatment guidelines. Acquisition cost, which will be affected by pricing and contracting scenarios, will be balanced against these clinical outcomes.

Achieving a proper balance is essential to lowing anticipated barriers to access (eg, prior authorization, step edits, etc) for FEBT. If a proper balance is unachievable within the commercial realities of FEBT, contracting should be limited to plans that place "not overly burdensome hurdles" to FEBT access by appropriate patients.

Efficient prescriber support overcomes prior authorization barriers

In those cases where plans require prior authorization, Cephalon will work with the plans (regionally and/or on a national level) to standardize the prior authorization forms and processes. Cephalon will utilize an array of communication channels to inform physicians of the prior authorization standards instituted by their local health plans such as detailing, telemarketing, and direct mail.

One of the most effective tools for overcoming the barrier of prior authorization has been the Reimbursement Hotline, which will be employed for FEBT as it was for ACTIQ. In addition, medical necessity forms and other support materials and service will be developed to reduce the paperwork burden and time requirements of getting reimbursement for patients with BTP who need FEBT.

FEBT STRATEGIC PATHWAY FOR MANAGED MARKETS

The managed markets strategy for FEBT will be executed in 3 major thrusts, as follows:

Phase I—Market Conditioning

The current definition of BTP is *a transitory exacerbation of pain that occurs on a background of otherwise controlled chronic pain. The phenomenon has also been labeled "incident pain" and "episodic pain." BTP can strike a patient quickly and without warning or it may have a more gradual onset before escalating to its maximum intensity.*

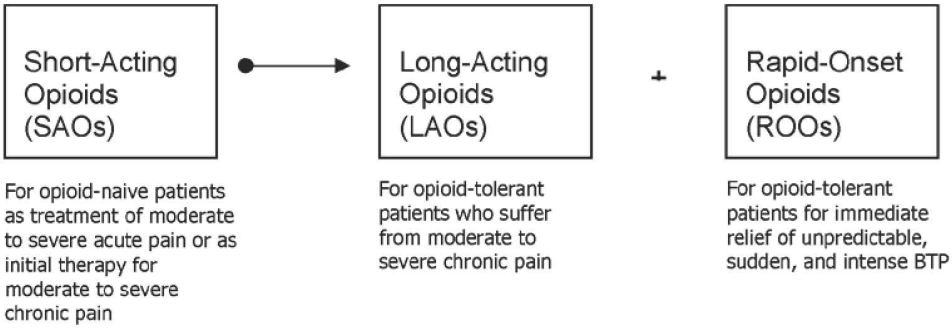
As precise as this definition appears it is still inadequate. BTP does not only "strike quickly and without warning," it is also often unpredictable. Its unpredictable nature is a primary reason why FEBT is an invaluable clinical tool. It can be taken anywhere, anytime, and without drawing unwanted attention to the situation.

Inserting "unpredictable" into the definition of BTP is a critical objective for Cephalon. It more precisely defines BTP as a more clinically challenging condition and better aligns its treatment with the clinical advantages of FEBT.

A key to success with managed care will be appropriate patient selection. This means that end of dose pain, which is typically included among the clinical situations leading to BTP, must be eliminated from the interpretation of BTP because it is not unpredictable and does not require a remedy having the BTP-specific analgesic profile of FEBT. Actively removing end of dose pain from the BTP profile reduces the risk that inappropriate patients would get FEBT, which should strengthen its value proposition by eliminating unnecessary costs for managed care plans. It will be easier for Cephalon to demonstrate the value of FEBT if patients who can effectively be managed with less expensive drugs (eg, titrating the LAO for end of dose pain) are eliminated.

As a natural next step, there will be an opportunity to revise the BTP treatment algorithm. Currently, physicians titrate SAOs to build opioid tolerance before switching patients to LAOs once it has been determined they suffer with chronic pain. For BTP, the physician essentially moves backwards to SAOs. The relatively slow onset and extended duration of effect make SAOs a poor choice for BTP. Patients often don't receive the pain relief they need at the beginning of BTP and become overmedicated after the pain subsides. For true BTP, Cephalon will support creation of the following treatment algorithm:

Revised Chronic Pain Management Algorithm (Including BTP)



Phase II—Conversion

Experts will characterize FEBT as the most elegant compound in the ROO category because of its faster onset of effect, more consistent and predictable absorption, and more discrete and convenient dosing as compared to a lozenge on a stick. These features, if connected to positive HEOR and clinical outcomes, will garner their support for and use of FEBT.

Phase III—Market Penetration

MCOs that cover FEBT will be surveyed to assess patient and physician satisfaction. Customer satisfaction parameters will include both economic impact estimates and QoL measures.

FEBT Strategic Map for Managed Markets

MANAGED MARKETS MESSAGE

The key messages for the managed care decision maker will be refined during the remainder of 2005 (see next section, Integrated Strategy Development Process).

Based on the current target product profile for FEBT and anticipated HEOR data, the message platform would be as follows:

Efficacy

- Rapid onset of action (although this will lack advantage to OTFC without the 3039 study data in the label at launch)
- Meaningful analgesic effect within 15 minutes (publication only until 3039 data added to the label)
- Efficacy for up to 120 minutes (publication only until 3039 data added to the label)

Pharmacokinetics

- Higher absolute bioavailability as compared to ACTIQ (65% vs. 47%)
- Greater portion of FEBT is absorbed through the buccal mucosa resulting in less first-pass metabolism compared to ACTIQ
- FEBT demonstrates higher early systemic exposure compared to ACTIQ (C_{max}, T_{max}, $AUC_{0\text{-}tmax}$)

Quick-dissolving tablet formulation offers benefits over lozenge formulations

- Compatibility with ambulatory setting
  - Discrete and inconspicuous
  - Nonlozenge form less likely to appear "attractive" to children
  - No "partially consumed" medication to secure from potential pediatric misuse
  - Easy to carry
- Consistent and predictable absorption
  - Not “technique dependent”

HEOR Benefits

- Effective management of BTP allows increases in physical activities that can promote recovery and rehabilitation
- Permits confident reengagement in the workplace and participation in activities of daily living
- Reduces utilization of costly medical services (eg, emergency room visits and hospitalization)

INTEGRATED STRATEGY DEVELOPMENT PROCESS

The strategies presented in this plan will be refined through the Integrated Strategy Development Process that will begin in Q3 ‘05 and be completed by Q1 ‘06. Throughout this process we will test and validate our assumptions and develop a clearer understanding of our ability to compete against the current standard of care (SAOs), ACTIQ, and generic OTFC in the managed markets arena.

Process

This process will help expand our understanding of formulary negotiations, including the following elements that are essential to presenting the most compelling value proposition possible to managed care customers and optimizing the formulary status of FEBT:

Target Product Profile

- Clinical effectiveness

- HEOR data providing evidence that FEBT positively impacts costs and improves clinical outcomes
- Comparative efficacy and safety vs standard of care (SAOs)
- Drug safety, including potential for abuse and diversion of prescriptions

Cost Management Strategies

- Price
- Rebates
- Value-added services (eg, specialty pharmacy services)
- Reimbursement level (tiers)
- Coinsurance
- Co-pay

Clinical Management Strategies

- Algorithms (treatment guidelines and edits)
- Prior authorization

Payer Strategies

- Variations within different books of business

Process Steps

The steps below outline the integrated research and strategic development process that will inform Cephalon's decision making regarding its investments in clinical research, promotional activities, value-added services, and contracting.

1) Managed Care Advisory Board Meeting (Surrogates)

Cephalon will convene a meeting of an advisory board composed of former managed care decision makers (surrogates).

The advisors will participate in a discussion of how MCOs and benefits managers structure pharmacy benefits and how pharmacy and medical directors might approach negotiations with pharmaceutical companies for a medication such as FEBT. All participants will be under contract as consultants to Cephalon and thereby bound by nondisclosure agreements that will allow them to see confidential clinical and marketing information, if necessary.

Follow-up Phone Contact

Advisors will be available by phone to address outstanding issues, as needed.

2) Managed Care Advisory Board Meeting in Conjunction With Fall 2005 AMCP Meeting

Cephalon will convene a meeting of an advisory board composed of about 10 managed care decision makers. The advisors will see presentations and participate in a discussion of the following topics:

- Nature and clinical presentation of BTP
- Burden of illness associated with chronic pain and BTP
- Effect of BTP on QoL and productivity in patients with chronic pain
- Clinical challenge of managing BTP
- Pain products in development
- FEBT product profile
- The role of ROO (FEBT)

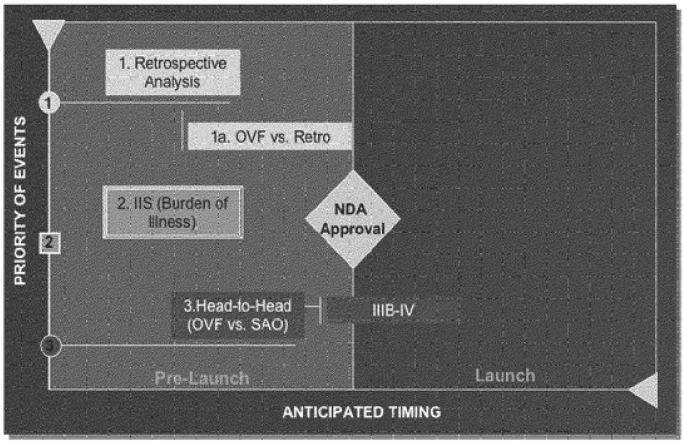
All participants will be under contract as consultants to Cephalon and thereby bound by nondisclosure agreements that will allow them to see confidential clinical and marketing information, if necessary.

Cephalon will provide honoraria, and reimbursement for incidental expenses. The half day meeting will be held October 5 in conjunction with the AMCP meeting. The meeting vendor will submit a written report of the advisory board meeting.

TACTICS

Phase I: Market Conditioning

Cephalon or Investigator-Initiated Phase IIB & IV Studies Conducted Within Key MCOs



1) Retrospective Analysis of Treatment of BTP

Description: Retrospective chart audit on an n^{th}-name basis to collect the following data:

- Patient diagnosis
- Pain history
- Treatment history
- Physician assessment of patient functionality (activities of daily living)

The physicians would also be interviewed and surveyed using a validated questionnaire. Ideally, patients or a segment of patients would also be interviewed so that their perspective could be compared and contrasted with that of the treating physician.

These data would form the basis of a published paper on the current state of science in the management of BTP.

2) Burden of Illness Assessment

Description: An assessment of the direct and indirect costs of BTP, looking at various parameters under the headings, utilization of medical services, and lost productivity and attendance at work.

3) FEBT vs SAO: Health Economic and Clinical Study in BTP Management

Description: An open-label trial comparing FEBT with SAOs in patients with nonmalignant BTP. This trial would compare the drugs with respect to time to complete pain relief, patient utilization of medical services, patient productivity and attendance at work, and measures of patient satisfaction and comfort.

It is hoped that this trial would show that the superior clinical performance of FEBT returns personal and economic benefits.

Authoritative Treatment Guidelines

Cephalon will support the validation of recent consensus panel recommendations published by Bennett, Burton, and Fishman, et al, in the June 2005 issue of *P&T*. The experts involved in the validation will assist in the dissemination of all published and presented clinical information concerning the results.

Funding for this effort will be handled through an unrestricted grant; therefore, the group's output will not be under the control of Cephalon.

Phase II: Conversion

KOL Leader Development

Cephalon will continue to develop relationships with KOLs specializing in pain management. KOLs will assist Cephalon in the following areas related to managed markets:

- Validation and dissemination of treatment guidelines
- Interface with USP to support the subcategorization of ROOs
- Educating Managed Care regarding appropriate BTP assessment and treatment
- Achieving favorable reimbursement status

Public Relations

Cephalon will work with a public relations firm to raise Managed Care awareness of the clinical and personal challenges of BTP. It is important that payers are sensitized to the needs of the chronic pain sufferer who endures BTP. The PR message must include the following:

- The personal and clinical challenges of BTP
- The latest breakthrough in effective treatment
- The consequences of inadequate or inappropriate treatment
- Inadequate pain management is not only cruel, but also bad health economics
- The value proposition for FEBT (commercial- and government-sponsored managed care has a responsibility to cover/reimburse for effective pain management)
- As always with a CII medication, Cephalon must ensure that FEBT is used safely

Managed Care Pharmacy and Medical Director Advisory Boards

Cephalon will conduct a series of Advisory Board meetings with managed care decision makers across the country. These meetings will provide an opportunity

to discuss issues that are important to the clinical and commercial success of FEBT, including the following:

- Appropriate use and patient selection
- Use by various physician specialties
- Clinical guidelines
- HEOR benefits
- Pricing and other access criteria (eg, prior authorization, step edits, tiered reimbursement)

These meetings will begin in 1Q '06 and continue through Q4 '06.

Petition USP

In April of this year, the Centers for Medicaid and Medicare Services (CMS) began reviewing formulary proposals from commercial health plans based on the drug classification guidelines developed by USP. This drug classification system includes 146 drug classes. CMS requires that every formulary serving Medicare and Medicaid recipients must offer access to at least 2 drugs from each class, more in some cases.

A petitioning process will be put into place by USP sometime in the summer of 2005 for people who wish to alter the classification system in any way. Once the process has been established, Cephalon will petition the USP to designate ROOs as a separate drug class within the system. It is anticipated that this will impact all commercial formularies.

HECON Impact Model

This computerized model will be developed based on HECON clinical data compiled from the literature, Cephalon-sponsored clinical trials, and investigator-initiated clinical trials of FEBT. This model will allow Cephalon managed markets executives to demonstrate the economic impact of FEBT on a plan.

"Cost of Pain" Speaking Tour

This series of speaking engagements with the pharmacy managers, medical directors, and case managers will make the point that poorly managed BTP costs money and harms their patients. The presentations, given by KOLs/MSLs, will cover the following:

- Description of BTP
- Burden of Illness for BTP
- Proper pain management (LAO + ROO)

- HECON benefits of proper pain management
- Economic impact of providing ROO
  - Productivity
  - Attendance
  - Reduced utilization of medical services
  - Fewer claims for worker's compensation

Academy of Managed Care Pharmacy (AMCP) Exhibits and Activities

Cephalon will exhibit at AMCP meetings each year. These meetings will provide an opportunity for managed markets executives from Cephalon to interact with key managed care decision makers across the country. Activities should include the following:

- Advisory board update meetings
- Commercial exhibits (eg, "BTP: The Price of Pain")
- Scientific symposia
- Scientific posters
- Social events

Phase III: Market Penetration

FEBT Dossier

Cephalon will develop an FEBT Managed Care Dossier in the standard format as established by the AMCP. This dossier will be the primary tool for securing favorable reimbursement status.

Pull-Through Programs

Once a favorable contract has been established between Cephalon and a plan, Cephalon sales representatives will educate physicians and other healthcare provider staff regarding reimbursement status and requirements for coverage.

Prior Authorization and Medical Necessity Assistance Program

Many plans may opt not to cover FEBT without prior authorization. Cephalon will assist physicians who have patients in plans requiring prior authorizations and letters of medical necessity. Cephalon will work with these plans to establish the kinds of information and support that are required to receive authorization and optimal reimbursement. Cephalon will work with the major health plans on a national and regional level to standardize the PA process to simplify the process for healthcare providers. Cephalon will develop guidelines for the representative and for physicians, with accompanying forms, to facilitate authorization by each plan.

Patient Support

Cephalon will continue to offer and further develop the Emerging Solutions in Pain program.

Continue Clinical Development

Expanded Labeling

It is essential to the value proposition of FEBT that data to support differentiation from current competitors and its utility in nonmalignant BTP be proven. The number of patients with BTP secondary to nonmalignant chronic conditions is significantly larger than the cancer population with BTP and represents a significant clinical and commercial opportunity for FEBT.

The clinical research group will develop a sNDA for inclusion of the Study 3039 data supporting rapid onset of pain relief in cancer patients with BTP and to expand the label indication to include nonmalignant BTP. This approval will help expand reimbursement coverage by plans who limit FEBT reimbursement to FDA-approved label indications and strengthen the value proposition of FEBT.

Published Studies

All clinical trial data (in both malignant and nonmalignant cancer pain) will be published as soon as possible to support the value proposition for FEBT and secure favorable reimbursement.

PLAN INTEGRATION

Phase I	*Phase II*	*Phase III*
Strategy		
Define BTP & Realign Treatment Algorithm	*Rapid & Reliable Treatment for BTP*	*Patient and Payer Satisfaction*
Critical Success Factor		
• Authoritative treatment guidelines that recognize BTP and ROO as preferred treatment • Comprehensive HEOR support for treatment of BTP with ROO	• Value proposition of ROO established in treatment of BTP • FEBT value proposition embraced by key managed market decision markers (*outcomes + price + contracts*)	• Coordinated pull-through program that optimizes managed care opportunity • Efficient prescriber support overcomes prior authorization barriers
Tactic		
1) Advisory Boards 2) Validate guidelines 3) Customer Pricing Study 4) Retrospective Study of BTP Treatment (assess burden of BTP) 5) Establish ROO in literature 6) Conduct clinical trial ROO vs. SAO 7) Establish validated chronic pain assessment tool which includes BTP component 8) Conduct HEOR initiatives	1) Phase IIIB/IV: FEBT vs. retrospective data 2) Petition USP for ROO classification 3) MSLs conduct formulary review discussions 4) HEOR impact model 5) "Cost of Pain" speakers program 6) Managed care selling materials (eg, Dossier, FEBT Slide Kit) 7) Advisory board meetings	1) Pull-though programs 2) Prior authorization and medical necessity support program, office staff training program 3) Provider advisory boards 4) AMCP exhibits and educational programs 5) Call center initiatives 6) Continued patient support (Emerging Solutions in Pain) to encourage appropriate and safe use of FEBT

Appendix 3 – FEBT Development Plan

TABLE OF CONTENTS

I. Summary

Indication(s); Breakthrough Pain in Cancer Patients (BTP-C), Breakthrough Pain in Noncancer Patients (BTP-NC)

Filing Dates: US NDA – August 2005 (BTP-C), US sNDA – 3Q '06 (BTP-NC), EU MAA – TBD

Clinical Status: Phase III BTP-C

Launch Timing: 3Q '06 (BTP-C), 4Q ' 07 (BTP-NC)

Manufacturing: API; Johnson Matthey, Formulation and packaging; Salt Lake City (CIMA Eden Prairie secondary facility)

Key Project Issues and Risks: Negotiation of Risk Management Plan, timely recruitment of patients for open-label study (99-15), launch timing following approval. Launch concurrent with Barr generic ACTIQ® entry.

In August 2004, Cephalon acquired CIMA LABS INC. (CIMA) and with the acquisition the OraVescent® fentanyl (FEBT) technology. FEBT is the registered trademark name for the oral transmucosal drug delivery system developed by CIMA. FEBT is patent protected. The United States patent estate protecting FEBT brand oral transmucosal fentanyl citrate comprises issued patent US 6,200,604, expiring March 26, 2019, and 6 filed pending patent applications. Additional patent protection for methods of manufacturing and packaging comprises U.S. 6,155,423, expiring April 1, 2018, and 3 filed pending patent applications.

The unique FEBT formulation contains bicarbonate which produces effervescence when placed in the mouth. The release of carbon dioxide acts as an absorption enhancer. The carbon dioxide reduces the thickness of the mucosal layer, opens tight junctions, increases hydrophobicity of the cell membrane, and gradually changes the pH of the microenvironment which facilitates absorption through the mucosa. Fentanyl, which is a poorly soluble weak base, has limited oral bioavailability (<33%) from the gut wall metabolism and extensive hepatic metabolism. The rapid and more complete absorption through the oral mucosal provided by the FEBT technology increases the potential for the dosage form to perform better than traditional oral dosage forms. Additionally, FEBT may have inherent advantages over the existing ACTIQ® oral transmucosal fentanyl product. FEBT should be easier for the patient to use, may reduce user error, and have higher bioavailability, allowing for lower doses to be effective compared to ACTIQ®. The absence of the stick allows the patient to avoid the stigma and eliminates the "lollipop" look that has raised concerns regarding pediatric exposure with ACTIQ®.

At the time of the acquisition, the Phase III efficacy and safety trials for FEBT were in progress. The clinical trials supported label claims identical to the existing ACTIQ® label. With the knowledge of the breakthrough pain (BTP) market, a 2-phase approach to development and regulatory submission is being executed for FEBT. The first phase of the strategy is to file an NDA for the FEBT dosage form with an indication to manage BTP in opioid-tolerant patients with cancer, followed by submission of a sNDA for an indication to manage BTP in opioid-tolerant patients with chronic noncancer pain. The initial filing would include the existing studies initiated by CIMA and an additional efficacy study to evaluate onset of analgesia. Four additional Phase I studies to characterize the pharmacokinetics, bioavailability, and support titration schemes will be conducted and included in the initial NDA. The studies necessary for an expanded indication in BTP associated with chronic, noncancer pain will be initiated in the first quarter of 2005, with the intent of having an sNDA ready for filing upon approval of the original NDA in 3Q '06. This time

line provides the noncancer BTP data available to address medical inquiries near the launch of the product with the breakthrough cancer pain indication.

On October 16, 2003, CIMA and Taiho executed a Development and License Option Agreement. On July 31, 2004, a Data Access Agreement between CIMA and Taiho was signed for CIMA to conduct Phase I studies to support the Japanese registration. The Phase I studies are being conducted in the United States in Japanese nationals. The subsequent studies required for registration will be conducted by Taiho in Japan. Cephalon will review Taiho's protocols to ensure they also support Cephalon's interests.

II. FEBT Target Product Profile

Indication

First indication: For the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Expanded indication: FEBT is indicated only for the management of breakthrough pain (BTP) in patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

Contraindications, Warnings, and Precautions

- Same as ACTIQ® except for pediatric and diabetic warnings and disposal instructions, which are not expected for this formulation.
- May have warnings about tampering with the formulation and misuse.

Pharmacokinetics

- Absorption information based on relative/absolute Bioavailability Study.
- The PK data (C_{max}, AUC, and t_{max}) on proposed marketing strengths of 100, 200, 400, and 800 mcg will be described within a table.
- In the studies conducted with FEBT and ACTIQ® the t_{max}, for ACTIQ® was ~2 hours, while for FEBT it was 45 minutes. This is with venous sampling. T_{max} with arterial sampling will also be included in the label. T_{max} with arterial sampling is what is in current ACTIQ® label. In the label, the t_{max} for FEBT will be included, but the ACTIQ® t_{max} will most likely not be in the label.

Clinical Trials

- Study 099-014, Efficacy of FEBT in opioid-tolerant cancer patients with BTP
  - Proportion of patients achieving a "successful" dose
  - Distribution of patients by successful dose
  - Result from $SPID_{0-30}$
  - Graph of PID over time (15, 30, 45, 60 minutes)
- Study 3039, Efficacy of FEBT in opioid-tolerant cancer patients with BTP
  - Proportion of patients achieving a "successful" dose
  - Distribution of patients by successful dose (may combine with previous study)
  - Result from $SPID_{0-60}$
  - Graph of PID over time (5, 10, 15, 30, 45, 60, 90, 120 minutes)
  - Onset of meaningful pain relief is within 30 minutes for the majority of patients.

Safety

- AE profile similar to ACTIQ®
- Number of opioid-tolerant cancer patients studied (~500)
- Average duration of treatment in Open Label Extension Study (099-15)
- AE table from the titration phases of 099-014, 3039, and new patients in 099-015
- AE table from long-term Open Label study (099-15)

> AE table from switching study after the switch from ACTIQ® to FEBT

Special Populations

> Pharmacokinetic and adverse event information in patients with mucositis with any AE information

Dosage and Administration

See Appendix I for full proposed DOSING AND ADMINISTRATION section of FEBT package insert.

> All patients need to be opioid tolerant.

> Patients should start on 100 mcg with the exception of patients previously receiving ACTIQ® at doses >600 mcg.

> In adult patients previously receiving ACTIQ® for BTCP, the initial episode dose of FEBT should be as shown in the table below:

Current ACTIQ® dose (µg) per BTCP Episode	FEBT Initial Titration Dose (µg)
200	100
400	100
600	100
800	200
1200	400
1600	600

> Dose titration instructions will be similar to those of ACTIQ®.

- Place tablet between upper cheek and gum.
- Should take 15 minutes to dissolve – can be swallowed if not completely dissolved after 30 minutes. Rub cheek area over the unit if the unit is not dissolved fully after 15 minutes.
- Don't drink or eat while in mouth.
- If excessive signs of opioid effects appear – spit out.
- Swallowing may result in lower peak concentrations.
- Redosing within a single episode:
  - 30 minutes after start of previous tablet
  - Second dose should not exceed initial dose level.
- Increasing the dose:
  - The dose should only be increased to the next higher dosage level until the patient reaches a dose that provides adequate analgesia for a BTCP episode.
  - Dosage strengths should not be skipped.
  - Multiple tablets may be used to produce mcg equivalents to available doses.
  - Evaluate dose over several episodes (1 to 2 days)

- Side effects more frequent during this initial titration phase

- Daily limit:
  - Treat four or fewer episodes per day.

III. Regulatory Strategy

CIMA filed IND 65447 for FEBT citrate in July 2002. A pre-IND meeting was conducted with the FDA in November 2001. An End of Phase II meeting was conducted in December 2003. Ownership of the IND was formally transferred from CIMA to Cephalon, Inc. in October 2004.

The NDA for FEBT will be submitted in August 2005 for a BTP indication in opioid-tolerant patients with cancer. A pre-NDA meeting for the first submission is planned for April 2005. The safety data on 500 unique patient exposures with 50% of these receiving higher doses (>600 mcg) requested by FDA will be included in the initial NDA submission.

The NDA will include a complete Quality section to support the novel FEBT dosage form. To support continuity of product supply, 2 manufacturing and primary packaging sites will be submitted. The 2 facilities are Eden Prairie, Minnesota, and Salt Lake City, Utah.

In September 2004, Cephalon conducted an End of Phase II meeting with the FDA to discuss expanding the ACTIQ® indication to include managing BTP in opioid-tolerant patients with chronic noncancer pain. The label expansion will be pursued for FEBT. The working premise is that the agreements with FDA regarding ACTIQ® will apply directly to FEBT. Cephalon will request confirmation of those agreements from the FDA relative to an expanded label for FEBT. The expanded label will be filed as a sNDA once the NDA has been approved. It will contain data from a 12-month safety study and 2 efficacy studies. The FDA has requested that the submission contain 300 to 500 noncancer patients treated for 6 months and 100 patients treated for 1 year. This must be part of the sNDA at the time of submission and cannot be submitted at a later update.

A critical component of the development, approval, and commercialization of FEBT is the Risk Management Program (RMP). While it is likely that the RMP for FEBT will, similar to ACTIQ®, focus on preventing/minimizing (1) abuse and diversion, (2) accidental ingestion (primarily by children), and (3) improper patient selection (opioid–non-tolerant patients), it is also likely that, given the characteristics inherent in FEBT and the heightened external concerns about opioid-prescribing, the RMP will focus more significantly on abuse and diversion issues, with less focus on accidental ingestion. Further, given the recent FDA Risk MAP guidance, it is expected that the RMP will have more areas where the Company is expected to provide the Agency with measurable data on risk-minimization activities. Therefore, while the RMP will continue to focus on prevention, education, monitoring, and intervention (also similar to the ACTIQ® RMP), there will be significantly more focus on measuring the success of the RMP. Agency guidance will be sought at the upcoming pre-NDA meeting, and it is expected that negotiations on the particulars of the RMP will continue throughout the approval process.

IV. Preclinical Development

At the September 2004 End of Phase II meeting with the FDA to discuss an indication for noncancer BTP, Cephalon requested concurrence from the agency that the ACTIQ® toxicology data, currently included under NDA 20-747, are adequate to support the proposed indication noting that NDA 20-747 is a 505(b)(2) application referencing Duragesic's NDA 19-813 that is not supported by a carcinogenicity study. It is expected that FDA response regarding ACTIQ® is relevant to the FEBT NDA and sNDA which will be confirmed at the appropriate FDA meetings for both cancer and noncancer BTP. For the adult population, the FDA encouraged Cephalon to conduct fertility/reproduction studies in male rats (Segment I), pre- and postnatal development

study (Segment III), and 2-year carcinogenicity studies in 2 species. In the meeting and documented in the minutes, Cephalon stated that they understood that carcinogenicity studies were encouraged but not required. FDA stated that carcinogenicity studies would probably be necessary to support extension of the new indication into a population of pediatric patients without malignancies. At this time, Cephalon has no definitive plans to conduct these studies for inclusion in the initial NDA for BTP in cancer patients nor the subsequent sNDA for noncancer pain BTP.

V. Clinical Development Plan

As described previously, the Clinical Program will support a cancer and a noncancer BTP indication filed in 2 separate regulatory submissions.

At an End of Phase II meeting for ACTIQ® in noncancer BTP, the FDA communicated the requirement for full ICH guideline safety exposure, specifically in the noncancer patient population. The time to recruit and treat for the 1-year exposure requirement does not allow for a single NDA containing the required data for an indication in both populations to be submitted in time to ensure approval prior to generic entry for ACTIQ®. Hence, to facilitate approval of the NDA prior to generic entry, the BTP in cancer patients will be filed first in August 2005. To maximize commercial opportunity, the noncancer BTP studies will be initiated in 1Q '05, with the data available to file an sNDA after initial approval, and available to address medical inquiries near the launch of the product with the breakthrough cancer pain indication.

The current ACTIQ® labeling describes the t_{max} for fentanyl occurring between 20 and 40 minutes. Arterial plasma sampling was done in the ACTIQ® studies that generated these data. Subsequent pharmacokinetic data generated for ACTIQ® and FEBT has used venous sampling. The t_{max} from these subsequent studies has been generally greater than 50 minutes, with the head-to-head comparison studies containing both FEBT and ACTIQ®, revealing t_{max} values of 2 hours for ACTIQ® and 1 hour for FEBT. These discrepancies reveal the importance of describing within the labeling the source of the plasma samples in order to understand the differences in t_{max} between the ACTIQ® label and the eventual FEBT label. As part of the labeling changes for the sugar-free formulation of ACTIQ®, a clarifying statement explaining that the PK parameters are from arterial sampling should be added to the ACTIQ® label. A similar statement should be included in the eventual FEBT labeling. In addition, publications of the FEBT PK studies evaluating both ACTIQ® and FEBT will be useful in pointing out that FEBT is actually faster than ACTIQ® in reaching t_{max}. The following sections outline the clinical studies to support each indication and tables mapping target promotional claims to the specific studies which will support those claims. Appendix 2 contains a more detailed overview of the clinical studies.

Breakthrough Cancer Pain Clinical Program

The first NDA for BTP in opioid-tolerant cancer patients will include results from 6 clinical pharmacology trials and 4 clinical safety and efficacy trials. The FDA has requested that there be 500 unique patient exposures with 50% of these receiving higher doses (>600 mcg).

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
099-11 – Dose Proportionality	Healthy volunteers	FEBT 270, 810, 1080, 1300 mcg ACTIQ® 1600	42	Establish the PK profile of FEBT	C_{max}, AUC, t_{max}	---	Complete
099-18 – Dose Proportionality	Healthy volunteers	FEBT 200, 500, 810 mcg	27	Determine if dose strengths proportional	C_{max} AUC	---	Complete
1028 – Absolute/ Relative Bioavailability	Healthy volunteers	FEBT 800, ACTIQ® 800, Fentanyl Inj, Fentanyl PO Sol.	24	Determine the absolute and relative bioavailability of fentanyl delivered via FEBT	AUC	1Q '05	2Q '05
1026 – BE of multiple lower doses vs. higher ones	Healthy volunteers	FEBT 100 and 400 mcg	24	4x100 mcg is equivalent to 1x400 mcg	C_{max}, AUC, t_{max}	1Q '05	2Q '05
1029 – Multiple Dose PK	Healthy volunteers	FEBT 400 mcg	24	Determine the steady state (ss) kinetics of FEBT	C_{maxss} and C_{minss}	1Q '05	2Q '05
1027 – Dose Proportionality	Healthy volunteers	FEBT 100, 200, 400, 800 mcg	24	Determine the PK characteristics of doses and show proportionality	C_{max} and AUC	1Q '05	4Q '05
099-16 – Safety	Cancer patients with mucositis	FEBT 200 mcg	18	Determine if PK of FEBT is altered in this population	C_{max}, AUC, t_{max}	4Q '04	2Q '05
099-14 – Efficacy	BTP cancer	FEBT and PBO	120	Determine the efficacy of FEBT	$SPID_{0-30}$	2Q '04	1Q '05
099-15 – Open Label 12-month Safety	BTP cancer	FEBT 100-800 mcg	400	Safety	Safety	2Q '04	2Q '05
3039 – Onset of Analgesia	BTP cancer	FEBT and PBO	100	Determine the efficacy of FEBT	$SPID_{0-60}$	1Q '05	2Q '05

Noncancer BTP Clinical Program

The sNDA for BTP in opioid-tolerant patients in a broad population will include 3 clinical studies, 2 efficacy studies and 1 open-label safety study. The 2 efficacy studies have similar design but 2 different populations. One study will recruit patients with low back pain; the second study will recruit patients with neuropathic pain from varied origin. The safety study will enroll patients with a variety of pain etiologies.

Study	Population	Treatments(s)	N	Primary Objective	Primary Outcome	FPFV	Results Available
3041 Efficacy Study	BTP – neuropathic pain	FEBT and PBO	100	Determine the efficacy of FEBT	SPID 0-60	3Q '05	2Q '06
3042 – Efficacy Study	BTP – low back pain	FEBT and PBO	100	Determine the efficacy of FEBT	SPID 0-60	3Q '05	2Q '06
3040 – 12-mo Open-Label Safety Study	BTP – chronic noncancer pain	FEBT	750	Safety	Safety	1Q '05	3Q '06

Supportive Studies

Several Outcome studies are being discussed for market support in the broader indication.

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
Health Economics	Chronic pain	FEBT and Percocet		Determine the efficacy FEBT has better patient outcomes	Function		
Efficacy	Chronic pain	FEBT, Percocet, and PBO		Determine the duration of effect for FEBT	Time with >50% rescue		
Efficacy	Chronic pain	FEBT and MSIR		Relative analgesic efficacy	SPID		

Studies for Taiho

CIMA is under contract to conduct the following Phase I studies to support the Japanese Registration Program. The Phase 1 studies will be conducted in the United States in Japanese nationals. The subsequent studies required for registration will be conducted by Taiho.

Study	Population	Treatments(s)	N	Primary Objective(s)	Primary Outcome	FPFV	Results Available
099-19 – PK	Healthy Japanese	FEBT 100, 200,	28	Establish the PK profile of FEBT in	C_{max}, AUC,	3Q	4Q '04

profile	volunteers	400, 800		Japanese volunteers	t_{max}	'04	
099-20 – MD PK	Healthy Japanese volunteers	FEBT 200 and 400 mcg	20	MD PK profile of FEBT in Japanese volunteers	C_{maxss}	4Q '04	2Q '05
099-21 – PK of Sequential dosing	Healthy Japanese volunteers	FEBT 200 and 400 mcg	20	PK profile of giving 2 doses FEBT simultaneously or sequentially	C_{max} and AUC	1Q '05	3Q '06

Additional Studies to Be Developed

- Consistency of plasma levels compared with ACTIQ®
- Duration of analgesia in chronic pain
- Relative potency
- Abuse liability
- Tampering
- Studies to support Risk Management Program

Clinical Studies Time Lines

Indication for BTP in Cancer				
Study	Protocol	FPFV	LPLV	Results
099-11 – Dose Proportionality	Jul 03	July 03	Aug 03	Sep 03
099-18 – Dose Proportionality	Oct 03	Nov 03	Dec 03	Mar 04
099-14 – Efficacy	Jul 03	Jul 03	Jan 05	Mar 05
099-15 – Open Label 12-Month Safety	Oct-03	Nov 03	May 06	Jun 05
099-16 – Safety Mucositis	Oct 04	Jan 04	Apr 05	Jun 05
3039 – Onset of Analgesia	Nov 04	Jan 04	May 05	Jun 05
1027 – Dose Proportionality	Nov 04	Jan 05	Jan 05	Apr 05
1028 – Absolute Bioavailability	Dec 04	Jan 05	Feb 05	Apr 05
1029 – MD PK	Dec 04	Feb 05	Mar 05	May 05
1028 – BE of Multiple Lower Doses vs Higher Ones	Jan 05	Mar 05	Apr 05	Jun 05

Expanded Indication for BTP in Noncancer				
Study	Protocol	FPFV	LPLV	Results
3040 – 12-mo Open-Label Safety	Nov 04	Feb 05	Jun 06	Jul 06
3041 – NPP	Jan 05	Mar 05	Sep 05	
3042 – LBP	Jan 05	Mar 05	Sep 05	
Studies Supporting Taiho				
Study	Protocol	FPFV	LPLV	Results
099-19 – PK	-	3Q '04	4Q '04	4Q '04
099-20 – MD PK	Nov 04	1Q '05		
099-21 – PK Sequential Dosing	Feb 05	1Q '05		

Target Promotional Claims and Associated Studies

The following tables map the target claims to the specific clinical studies which support those claims:

Target Claims at the Time of First Launch – BTP in Cancer Patients

Claim	Supportive Study	Outcome Variable	Vehicle
FEBT is effective in managing BTP in opioid-tolerant cancer patients	099-14 – Cancer Efficacy 3039 – Cancer Efficacy	$SPID_{0-30}$, Graph of PID over 60 min	Label
Time of analgesic onset with FEBT is <15 minutes	3039 – Cancer Efficacy	Stopwatch† and PID at 5 and 10 min*	Label*/ Promotional†
Time between BTP episodes after treatment with FEBT was on average >6 hrs while the time between events after treatment with PBO was less	099-14 – Cancer Efficacy 3039 – Cancer Efficacy	Time between BTP episodes	Promotional
FEBT is superior to PBO in controlling pain through 2 hours	3039 – Cancer Efficacy	PID scores through 2 hours postdose	Label

Claim	Supportive Study	Outcome Variable	Vehicle
There is dose proportionality among the dose strengths.	Dose proportionality Studies 099-18 and 1027	C_{max} and AUC values	Label
After 1 year of treatment with FEBT xx% of patients continued to achieve good pain control	099-15 – Cancer Safety Study	Global evaluation of efficacy	Promotional
Patients switching from ACTIQ® to FEBT should be placed on 1 dose below half the ACTIQ® dose (ie, 800 ACTIQ® is 200 FEBT)	1028 – Absolute Bioavailability Study 099-15 – Cancer Safety 3039 – Cancer Efficacy	Safety and efficacy observed after switching paradigm employed C_{max} and AUC values	Label
Of the patients switched from ACTIQ® to FEBT xx% required a dose increase, yy% required a dose decrease and zz% required no further adjustment in dose	3039 – Cancer Efficacy 099-15 – Cancer Safety Study	Dose of FEBT at the time of randomization in DB phase	Label
The majority (xx%) of patients preferred FEBT over previous BTP medication.	3039 – Cancer Efficacy 99-015 – Cancer Safety Study	Preference questionnaire administered at the end of the study	Promotional

Target Claims at the Time of the Second Launch With Expanded Indication

Claim	Supportive Study	Outcome Variable	Vehicle
FEBT is effective in managing BTP in opioid-tolerant chronic noncancer pain patients	3041 – NPP efficacy 3042 – LBP efficacy	$SPID_{-0-60}$, graph of PID over 60 min	Label
Time of analgesic onset with FEBT is <15 minutes	3041 – NPP efficacy 3042 – LBP efficacy	Stopwatch† and PID at 5 and 10 min*	Label*/ Promotional†
Time between BTP episodes after treatment with FEBT was on average >6 hrs while the time between them after treatment with PBO was less	3041 – NPP efficacy 3042 – LBP efficacy	Time between BTP episodes	Promotional
FEBT is superior to PBO in controlling pain through 2 hours	3041 – NPP efficacy 3042 – LBP efficacy	PID scores through 2 hours postdose	Label
After 12 months of use xx% of patients still able to achieve adequate pain relief with FEBT	3049 – Open-Label Safety in chronic noncancer pain	% of patients still in study	Promotional

Additional Claims Desired

Claim	Supportive Study	Outcome Variable	Vehicle
The relative potency of FEBT to MSIR is 1:10-20	TBD	PID, pupil diameter	Publication
The duration of analgesic effect of FEBT is 6 hours	Patients with chronic OA pain	PID, PR, time to rescue	Publication
FEBT has less of a dwell time than ACTIQ®	TBD		

VI. Health Economics (HECON)

Objective: To provide economic justification and differentiation for FEBT vs competitors

> HECON measures are included in Noncancer Open-Label study (3040)
> Finalize HECON strategy for Noncancer BTP by Q2 '05

Challenges

- Reimbursement / Managed care
  - Increasing barriers anticipated
  - Generics
  - Unarticulated needs
- Need to bridge ACTIQ to FEBT

Opportunities

- Rapid onset
- Cross-functional pricing and reimbursement infrastructure
- Malignant + nonmalignant pain

Objectives	Tactic/Program*	Target Audience	Timing	Resource
P&RE issues identification	Input into P&RE Assessment	Brand	Q2 '05	Market Research HEOR RE
Value generation	Input into long-term safety study David Nash – Thomas Jefferson research Patient preference	Clinicians Managed care	Q4 '04 Initiate planning Q1 '05	HEOR Clinical Research Sci Comm Marketing Publications
Managed care support	Partnership/ Phase IV studies? Formulary kit/tools	Managed care Clinicians	Initiate planning Q2 '05	HEOR Marketing Clinical Research Prof Services

VII. Pharmaceutical Development

Drug Product Development Plan

The dosage form is designed using the proprietary FEBT technology. The formulation contains bicarbonate which produces effervescence when placed in the mouth. The release of carbon dioxide acts as an absorption enhancer. The carbon dioxide reduces the thickness of the mucosal layer, opens tight junctions, increases hydrophobicity of the cell membrane, and gradually changes the pH of the microenvironment, which facilitates absorption through the mucosa. Fentanyl, which is a poorly soluble weak base, has limited oral bioavailability (<33%) because of gut wall metabolism and extensive hepatic metabolism. The rapid and more complete absorption through the oral mucosal provided by the FEBT technology increases the potential for the dosage form to perform better than traditional oral dosage forms.

Five commercial doses (100, 200, 400, 600, and 800 mcg) were developed. In December 2003, 2 batches of each strength were manufactured at the Brooklyn Park Facility. The material was used to support clinical trials, and stability was initiated for all strengths by February 1, 2004. The batch size of 100,000 tablets represents greater than one-tenth scale of the purposed commercial batch size in the Eden Prairie, Minnesota facility. The 12-month stability data on these batches will be included in the August 2005 NDA submission.

In December 2004, site registration batches will be manufactured at the Eden Prairie facility. One full-scale 80-kg batch of each strength was manufactured, packaged, and placed on stability by January 2005.

In early 2005, site registration batches will be manufactured at the Salt Lake City, Utah, facility. One 22-kg scale batch of each strength will be manufactured, packaged, and placed on stability. Three-month stability data on these batches will be included in the August 2005 NDA submission.

All of the development batches were compressed with plain tooling. The commercial product will be debossed on 1 side with the Cephalon logo and a single digit representing strength on the opposite side.

Package Development Plan

The physical characteristics of the FEBT formulation require a high moisture-vapor barrier. The friability of the tablet requires proprietary handling technology to transfer the tablets from the tablet press to the packaging line, and prohibits the use of push-through blister package designs. These factors led to unit dose foil blister package materials with a peel-opening design.

The API fentanyl is a Class II narcotic with a high toxicity level, and requires child-resistant (CR) packaging. The intent is for the CR package to meet the F1 child-resistance level. The patient population for this product necessitates a package design that will concurrently comply with the senior-friendly protocol.

Several prototype opening designs were developed and tested for CR. The 3 passing designs were tested in Market Research focus groups with the intent to optimize a package that meets F1 and senior-friendly protocols. The proposed design is a 2X2 bend and peel blister card. The card achieved a 96% child-effectiveness rating and a 97% senior-effectiveness rating. Opening instructions which are concise and readily understood will be developed for the final package design.

Standard blister labeling includes trade name, active ingredient and strength, lot number, expiration date, company name, and bar code. Additionally, the individual blister cells need opening directions for the CR feature, a fragile statement, and the warning statement regarding addiction. The "habit-forming" statement is expected to be a requirement of the RMP and the purpose of the fragile statement is to minimize tablet damage by patients in the opening process. Labeling for the primary package will be proposed and discussed with the FDA at the pre-NDA meeting in April 2005. The proposed text fits on a 68X104 mm blister card in a perforated 2x2 configuration. While it is desirable to get agreement at the pre-NDA meeting, it is probable that the individual blister unit label will be negotiated as part of the RMP and labeling discussions with final copy at the time of NDA approval. Appendix 3 contains the material specifications for the blister card material and the label being proposed at the pre-NDA meeting.

The overall dimension and configuration of the final commercial blister card will be determined by the amount of real estate required for label copy on each blister cell. The dimensions impact package tooling equipment design and the purchase of that equipment is on the critical path for launch readiness. Technical Operations is evaluating contingency plans for a blister card larger than 68X104 mm card but no greater than 136 mm in length beyond which there is a significant impact to packaging line design and output. CR testing will be conducted on the final production equipment and blister configuration.

The proposal is for the commercial carton to contain 28 tablets. Labeling for the carton (secondary package) will also be proposed at the pre-NDA meeting. Specifications for the package insert and patient leaflet will be submitted with the NDA. It is expected that multiple patient leaflets will be required in each carton. That number will be determined by the titration schedule.

FEBT Drug Product Profile

Parameter	Description
Dosage strengths	100, 200, 400, 600, 800 mcg
Shape	**Round beveled-edge**
Colors	Dose — Color 100 mcg — White 200 mcg — White 400 mcg — Pink 600 mcg — Orange 800 mcg — Yellow
Tablet markings	Debossed with Cephalon "C" logo on 1 side and 1-digit strength-identifier code on other side (last digit of the NDC).
Trade Packages	Unit dose packaging (foil/foil) blisters 100 mcg — XX count — NDC 63459-541-XX 200 mcg — XX count — NDC 63459-542-XX 400 mcg — XX count — NDC 63459-544-XX 600 mcg — XX count — NDC 63459-546-XX 800 mcg — XX count — NDC 63459-548-XX
Sample Package	There are no sample packages for this product. Any sampling will use coupon/commercial product.

VIII. Market Development

FEBT provides Cephalon the opportunity to extend the pain franchise beyond the patent expiration of ACTIQ®. The novel dosage form has unique advantages which could translate to patient preference and possible faster therapeutic effect. Market development activities for FEBT are planned or already in process with the objective of launching FEBT for BTCP in 3Q '06, and for "relaunching" with an expanded label for BTP 1 year later. Because ACTIQ® is projected to lose patent protection in 3Q '06, it is vital that FEBT is ready for launch as soon as FDA approval is obtained.

The table below outlines the FEBT market development activities and time lines:

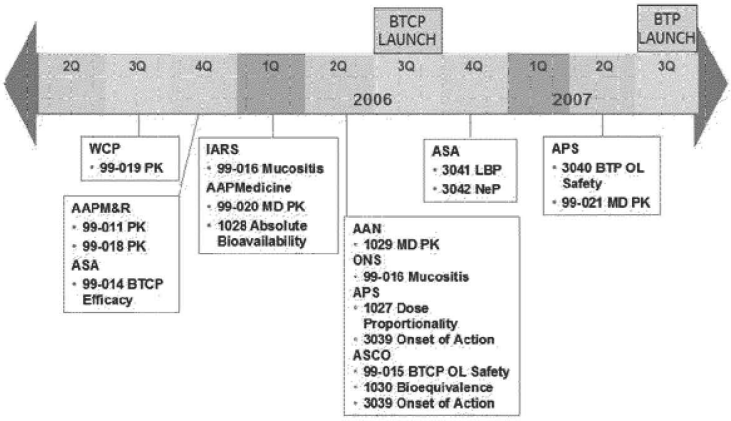
Activity	Description	Start Date	Completion Date
Trade name development	Vendor development of trade name options (final identification and registration by Cephalon TBD)	3Q '04	1Q '05
Package design	Identify the most cost-effective optimal package design that meets child-safety requirements, simplifies the titration process, convenient size and quantity to meet pharmacy/provider/patient needs	3Q '04	2Q '05
Communication plan development	Plan presents the communication strategy with regard to dissemination of key messages via publications, symposia, other media, and thought leader development	3Q '04	1Q '05 (Implementation of plan will be ongoing)
Preliminary marketing plan development	Comprehensive plan detailing initial product profile, key marketing issues, strategies, positioning, messaging, target audience, etc	4Q '04	1Q '05
Advertising agency selection	Selection of a strategic partner to effectively and efficiently prepare FEBT for commercialize	4Q '04	4Q '04
Creation and testing of branding elements	Creation of logo, color, and other branding elements	2Q '05	2Q '05
Development and testing of positioning	Creation of product position statement and its supporting messages	1Q '05	2Q '05
Thought leader development	Introduction FEBT to thought leaders, involve thought leaders in the clinical and commercial planning process	1Q '05	Ongoing
Managed care and third-party payers strategy	Determine contracting strategy to optimize FEBT reimbursement	3Q '05	3Q '06
Risk management program	Development of materials to meet RMP needs	1Q '06	3Q '06
Forecast refinement	Implementation of appropriate market research to refine FEBT forecast	4Q '04	Ongoing
Pricing	Identification of pricing strategy based on product attributes and projected market conditions via a pricing study	2Q '05	1Q '06
Market assessment	Ongoing tracking of the market and competitors	4Q '04	Ongoing

Activity	Description	Start Date	Completion Date
Campaign development	Creation, testing, and production of launch campaign materials	4Q '05	3Q '06
Sales force strategy	Identification of the optimal sales force size and alignment	1Q '05	Ongoing
Publication submission*	99-10 – PK		3Q '05
Publication submissions	99-011 – PK, 99-018 – PK, 99-014 – BTCP Efficacy		4Q '05
Publications submission	3039 – Onset of Action 99-016 – Mucositis 1027 – Dose Proportionality		2Q '06
Publications submission	99-015 – BTCP 0L Study 1028 – Absolute Bioavailability 1029 – MD PK		3Q '06
Publications submission	1030 – Bioequivalence 3041 – LBP		4Q '06
Publications submission	3042 – NeP		1Q '07
Publications submission	3040 – BTP OL Safety		3Q '07

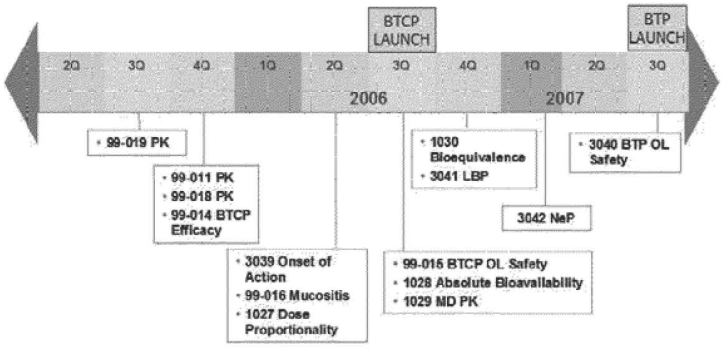
IX. Publications Strategy

The FEBT publications plan is designed to dovetail into the overall commercialization strategy and will capitalize on the Clinical Program. Its objectives and goals are to create a presence in the literature (both as congress abstracts and peer-reviewed journal articles) by communicating results of clinical research efforts, to communicate consistent messages across all submissions, and to establish potential advantages of FEBT in cancer and other forms of BTP. Messaging incorporated into the publications will be aligned with the desired claims. PK and clinical data will be rolled out as they become available, resulting in congress presentations and publications as the FEBT launch approaches. The illustrations below depict the time lines for presentations and publications developed out of the Clinical Program.

Congress Presentations Time Line



Publications Time Line

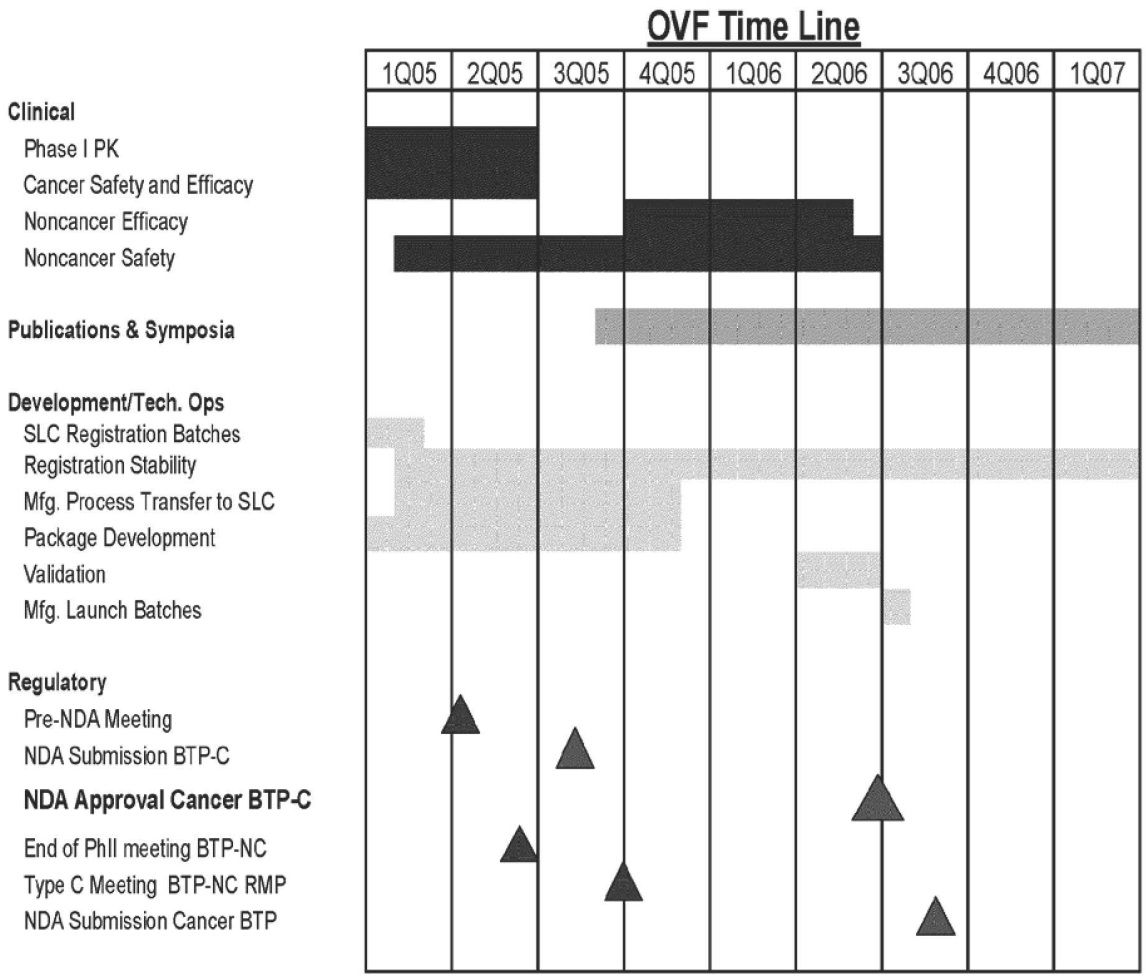


Because the expected target audience is composed of pain specialists and oncologists, congress choices are based on reaching these physicians as well as expected data availability. The target congresses for presentations in 2005 are the World Congress of Pain (WCP), American Academy of Physical Medicine & Rehabilitation (AAPM&R), and American Society of Anesthesiology (ASA). In 2006, the American Association of Pain Medicine (AAPM), International Anesthesia Research Society (IARS), American Academy of Neurology (AAN), American Pain Society (APS), Oncology Nursing Society (ONS), American Society of Clinical Oncology (ASCO), and the ASA will be targeted for submissions.

The journals targeted for manuscript submissions are primarily pain or oncology journals. Some of the PK study manuscripts will be directed towards pharmacology journals to broaden the audience receiving FEBT messages. Secondary/review articles intended to promote BTP

awareness are also planned for submission to further set the stage for the FEBT launch. In selecting appropriate journals, attention was given to journal scope, circulation, impact factor, submission to publication time, and acceptance rates. Consideration of these factors should allow timely publication of PK and clinical data in support of the FEBT launch.

X. Time Lines



Time line for NDA submission for indication in cancer BTP

Milestones	Target Start Date	Target Completion Date	Status
Pre IND Meeting	4Q '01	4Q '01	Complete
IND Filing	3Q '02	3Q '02	Complete
EOP 2 Meeting	4Q '03	4Q '03	Complete
Brooklyn Park Registration Batches	2Q '04	2Q '04	Complete
Initiate Brooklyn Park Stability	4Q '03	1Q '04	Complete
Eden Prairie Site Registration Batches	4Q '04	4Q '04	Complete
Pre-NDA Meeting	2Q '05	2Q '05	
Initial Efficacy Studies	2Q '04	4Q '04	Ongoing
SLC Registration Batches	4Q '04	1Q '05	Ongoing
Finalize Primary Package Specifications	3Q '04	2Q '05	Ongoing
NDA Submission	3Q '05	3Q '05	
Open-Label Safety Study	2Q '04	1Q '05	Ongoing
Onset of Action Study	1Q '05	1Q '05	Ongoing
Additional PK Studies	1Q '05	1Q '05	Ongoing
Additional Efficacy Trial – Onset	1Q '05	2Q '05	
Manufacture Validation Batches	2Q '06	2Q '06	
NDA Approval	3Q '06	3Q '06	
Launch	3Q '06	3/4Q '06	

sNDA Time line for submitting noncancer BTP

Milestones	Target Start Date	Target Completion Date	Comments
Pre-NDA Meeting	4Q '05	4Q '05	
sNDA Submission	3Q '06	3Q '06	
Open-Label Safety Study	1Q '05	1Q '06	
Efficacy Study – Low Back Pain	3Q '05	1Q '06	
Efficacy Study – Neuropathic Pain	3Q '05	1Q '06	
sNDA Approval	3Q '07	3Q '07	
Publication of Phase III Efficacy Data	1Q '07	1Q '07	

Appendix I

Draft Package Insert

DOSAGE AND ADMINISTRATION

FEBT is contraindicated in non–opioid-tolerant individuals.

FEBT should be individually titrated to a dose that provides adequate analgesia and minimizes side effects (see **Dose Titration**).

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

FEBT should be kept out of the reach of children. Patients should dispose of any tablets remaining from a prescription as soon as they are no longer needed. Unused tablets should be removed from their blister pouch and flushed down the toilet.

TABLET ACCESSING

Do not open the blister until ready to administer. For single tablet removal, separate one of the 4 blister units by tearing apart at the perforations. Bend the unit along the line where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

TABLET ADMINISTRATION

Using dry hands remove the tablet from the blister unit and immediately place the entire FEBT tablet between the upper cheek and gum. Patients should not attempt to split the tablet. The FEBT tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. The FEBT tablet should not be sucked or chewed. A tablet dose of FEBT, if chewed or swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The FEBT tablet normally dissolves within 15 minutes after placement. If after 30 minutes the FEBT tablet is not completely dissolved, it can be swallowed. If signs of excessive opioid effects appear before the tablet is completely dissolved, the tablet should be removed from the patient's mouth. Future doses may need to be decreased (see **Disposal of FEBT)**.

Patients and caregivers must be instructed that FEBT contains medicine in an amount that could be fatal to a child. Patients and caregivers should be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed (see **Disposal of FEBT**).

DOSE TITRATION

The initial dose of FEBT to treat episodes of BTCP should be 100 mcg. For patients already receiving ACTIQ, please see ***Conversion ACTIQ to FEBT****.*

From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *FEBT* dosage tablet per BTCP episode. Patients should record their use of *FEBT* over several episodes of breakthrough

cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Increasing the Dosage Level: Increases in the dose should be made until the patient reaches a dose that provides adequate analgesia for an episode of BTCP. During this titration phase the doses used should match those of the available strengths of FEBT. Available dosage strengths of FEBT are 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg. Dosage strengths should not be skipped. Multiple tablets may be used to produce mcg equivalents to available doses (see **PHARMACOKINETICS**).

Each new dose of *FEBT* used in the titration period should be evaluated over several episodes of BTCP to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Redosing Within a Single BTCP Episode: Patients may repeat dosing during a single episode of BTCP. The second dose should be equal to the strength of the initial dose taken during a BTCP episode. Redosing may occur 30 minutes after the start of the initial dosing during a single BTCP episode.

Daily Limit: Once a successful dose has been found, if patients experience greater than 4 BTCP episodes per day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.

Conversion ACTIQ to FEBT

It is important to recognize that patients using other forms of transmucosal fentanyl for BTCP cannot be switched to the same doses of FEBT. The pharmacokinetic profiles of other forms of transmucosal fentanyl are different from FEBT. In adult patients previously receiving ACTIQ® (oral transmucosal fentanyl citrate) CII for BTCP, the initial episode dose of FEBT should be as shown in Table X:

Table X

Current ACTIQ dose (µg) per BTCP Episode	FEBT Initial Titration Dose (µg)
200	100
400	100
600	100
800	200
1200	400
1600	600

DOSAGE ADJUSTMENT

Experience in a long-term study of FEBT used in the treatment of BTCP suggests that dosage adjustment of both FEBT and the maintenance (around-the-clock) opioid analgesic may be required in some patients to continue to provide adequate relief of breakthrough cancer pain. Generally, the FEBT dose should be increased when patients require more than 1 dosage tablet per cancer BTP episode for several consecutive episodes.

DISCONTINUATION OF FEBT

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

Appendix II

Overview of Clinical Studies

Efficacy 099-14 Pivotal Efficacy – Ongoing

Purpose: To serve as the pivotal efficacy trial for FEBT in cancer patients with BTP.

Objectives: To evaluate the analgesic efficacy and safety of FEBT vs placebo through the following measures:

- SPID at 0 to 30 minutes
- PID at 15, 30, 45, and 60 minutes
- PR at 15, 30, 45, and 60 minutes
- TOTPAR at 0 to 30 minutes
- Global evaluation of analgesic efficacy
- Evaluate the safety of FEBT

Study Design: The study design is nearly identical to that employed with the pivotal studies conducted with ACTIQ®. Patients are started on the 100-mcg dose and titrated to a successful dose. Once a successful dose (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is obtained, patients qualify for entry into the double-blind randomization phase. During this phase of the trial, patients will be randomized to receive a prespecified sequence of 10 blinded doses of study medication (7 FEBT and 3 placebos). After each dose, patients evaluate the analgesic efficacy of the treatment for 60 minutes. Rescue medication (oral immediate-release opioids) is permitted 30 minutes after the start of FEBT dosing. Patients completing the DB phase are permitted to enter the Open-Label Extension Study (099-15).

Population:

- N = 120 entered and 70 randomized
- Patients with cancer that have 1 to 4 BTP episodes per day
- On ≥60 mg/day of oral morphine or equivalent
- Currently receiving opioids for BTP
- Adverse events

Outcome Variables:

- Pain intensity
- Pain relief
- Global assessment of medication effectiveness
- Proportion of patients requiring rescue
- Time from study medication dose to next BTP episode

099-15 Cancer Open-Label 12-Month Safety – Ongoing

Purpose: To provide safety data on enough patients to meet the 500-patient exposure requirement set by the FDA at the End of Phase II meeting for FEBT.

Objectives:

- To evaluate the safety associated with longer-term (up to 12 months) use
- To evaluate the global analgesic effectiveness over time
- To evaluate the safety of switching ACTIQ®-treated patients to FEBT

Design: Open-label safety study lasting up to 12 months. Patients entering from the pivotal efficacy studies will continue into this trial on the successful dose previously established. This dose may be titrated up or down as required. For patients entering this study without previous exposure to FEBT, a titration paradigm similar to that conducted in the 099-14 Study will be performed. Those entering the trial on higher doses of ACTIQ® (800, 1200, or 1600) will begin administering the dose of FEBT at 1 dose below half the ACTIQ® dose (eg, subjects entering trial on 1200 mcg of ACTIQ® will begin dosing at 400 mcg). Visits in this study will occur monthly.

Patients:

- N ~400 entered (100 from the efficacy studies)
- Patients completing the 99-014 or 3039 studies or new patients meeting the same entrance criteria
- Patients with cancer that have 1 to 4 BTP episodes per day
- On >60 mg/day of oral morphine or equivalent

Outcome Variables:

- Safety
- Global evaluation of effectiveness
- Average dose at beginning and end of treatment
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study C25608/3039/BP/US Pivotal Efficacy

Purpose: To serve as an additional pivotal trial that generates data which can be used to differentiate FEBT from ACTIQ® (assessment of analgesia at earlier time points and onset of meaningful pain relief) and provide data on switching patients from ACTIQ® to FEBT.

Objectives:

- To evaluate the efficacy of FEBT vs placebo through the following measures:
  - Time to meaningful pain relief (stopwatch)
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 minutes and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - TOTPAR 0-60
  - Global Evaluation
  - Patient Preference
  - Safety

Study Design:

The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with FEBT in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. Those entering the trial on higher doses of ACTIQ® (800, 1200, or 1600 mcg) will begin dosing at a dose of FEBT that is 1 dose level below half the ACTIQ® dose (ie, patients entering the trial on 1200 mcg of ACTIQ® will begin dosing with FEBT at 400 mcg). All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, patients will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order for successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify when meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

> N = 100 entered and 70 randomized and evaluable
> Patients with cancer that have 1 to 4 BTP episodes per day
> On >60 mg/day of oral morphine or equivalent
> Currently receiving opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than one half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 1027 Dose Proportionality

Purpose: To determine if the PK profile of FEBT is linear across the dose range and to generate PK information on each strength of FEBT with the intent of having it described within the label as is done with ACTIQ®.

Objective: To determine the C_{max}, AUC, and t_{max} for each dose strength of FEBT (100, 200, 400, 800 mcg).

Design: Single-dose open label crossover

Population:

> N = 24
> Healthy volunteers

Outcome Variables:

> C_{max}, AUC, and t_{max}
> Plasma curves over a 6-hour period

Study 1026 Bioequivalence of four 100-mcg tablets to one 400-mcg tablet

Purpose: To establish the data necessary to allow patients to use multiple doses of 100 mcg to titrate to an effective dose, making the initial titration with FEBT more convenient.

Objective:

1. To determine if four 100-mcg tablets are bioequivalent to one 400-mcg tablet of FEBT
2. To determine PK profile of FEBT with arterial sampling

Design: Single-dose open-label crossover

Population:

- N = 24
- Healthy volunteers

Outcome Variables:

- C_{max}, AUC, and t_{max}

Study 1029 Multiple Dose PK

Purpose: To establish the steady state PK profile and determine if there is any dose accumulation

Objective: To establish the steady state PK profile of FEBT

Design: Single- and multidose open-label crossover

Population:

- N = 24
- Healthy volunteers

Outcome Variables:

- C_{maxss}, AUC_{ss}, and t_{maxss}

Study 1028 Absolute/Relative Bioavailability

Purpose: To determine the proportion of fentanyl absorbed via buccal mucosa compared to ACTIQ®

Objectives:

a. To establish the absolute bioavailability of the FEBT dose

b. To determine the relative bioavailability of FEBT to ACTIQ® and swallowed Fentanyl

Design: Single-dose open-label crossover with equivalent doses of IV fentanyl, oral solution of fentanyl, FEBT, and ACTIQ®

Population:

- N = 24
- Healthy volunteers.

Outcome Variables

- C_{max}, AUC, and t_{max}.

099-16 Tolerability and PK in Patients With Mucositis

Purpose: To obtain data on the use of FEBT in cancer patients with mucositis

Objective:
a. To evaluate the tolerability of FEBT in patients with mucositis
b. To evaluate the PK profile of FEBT when administered to patients with mucositis

Design: Single-dose open-label study

Population:

- N = 12
- Cancer patients who are opioid-tolerant and have mucositis

Outcome Variables:

- Mucosal irritation
- AEs
- C_{max}, AUC, and t_{max}

Study 3041 Neuropathic Pain Efficacy

Purpose: To serve as a pivotal efficacy trial in the submission for an expanded indication into BTP in patients with chronic, noncancer pain

Objectives:

- To evaluate the analgesic efficacy of FEBT vs placebo as measured by
  - SPID 0 to 60 minutes
  - Time to meaningful pain relief
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - Preference of FEBT compared to previous BTP medication
  - Safety

Design: The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with QVF in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, subjects will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order following successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify the time at which meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

- Chronic neuropathic pain of at least a 3-month duration from postherpetic neuralgia, diabetic peripheral neuropathy, chronic regional pain syndrome, and traumatic injury
- On >60 mg/day of oral morphine or equivalent
- Experience 1 to 4 episodes of BTP per day
- Currently taking oral opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than 1 half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 3042 Low Back Pain Efficacy

Purpose: To serve as a pivotal efficacy trial in the submission for an expanded indication into BTP in patients with chronic, noncancer pain

Objectives:

- To evaluate the analgesic efficacy and safety of FEBT vs placebo as measured by:
  - SPID 0 to 60 minutes
  - Time to meaningful pain relief
  - PID at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - SPID at 60 and 120 minutes
  - PR at 5, 10, 15, 30, 45, 60, 90, and 120 minutes
  - Preference of FEBT compared to previous BTP medication
  - Global assessment of medication performance
  - Safety

Design: The design of this study is nearly identical to that of the other efficacy trial, Study 099-14. After meeting entry criteria, patients will undergo an open-label titration with FEBT in order to identify a successful dose for each patient. The starting dose will be 100 mcg for most patients. All patients will be titrated up until a successful dose of FEBT (one that effectively controls 2 consecutive episodes of BTP without unacceptable adverse events) is found. Those patients who find a successful dose between 100 and 800 mcg will qualify for entry into the double-blind period of the study.

During the double-blind period of the trial, subjects will be randomized to receive a prespecified sequence of 10 doses of blinded study medication (3 placebos, 7 FEBT). They will be instructed to take the doses in a predetermined order following successive BTP episodes. Following each dose, patients will measure pain intensity, pain relief, identify the time at which meaningful pain relief is achieved, and provide a global medication performance assessment.

Population:

- > Chronic low back pain of at least 3 months' duration from osteoarthritis, degenerative disc disease, or spondilolysthesis with supportive radiographic evidence and a functional disability
- > On >60 mg/day of oral morphine or equivalent
- > Experience 1-4 episodes of BTP per day
- > Average episode lasts 4 hours or less
- > Currently taking oral opioids for BTP

Outcome Variables:

- Pain intensity
- Time to meaningful pain relief
- Pain relief
- Global evaluation of efficacy
- Time from study medication dose until next episode of BTP
- Proportion of patients previously using ACTIQ® who achieve successful treatment with FEBT at 1 dose level less than half the ACTIQ® dose
- Proportion of patients who prefer FEBT over their previous BTP treatment
- Adverse events

Study 3040 Noncancer Open Label 12-Month Safety

Purpose: To enroll enough patients to achieve a total of 300 patients treated for 6 months and 100 patients treated for 1 year

Objectives:

- > To evaluate the safety associated with longer-term (up to 12 months) use
- > Evaluate the global analgesic effectiveness over time
- > Evaluate the impact of FEBT on patient-reported outcomes

Design: Open-label safety study lasting up to 12 months. Patients entering from the pivotal efficacy studies in noncancer pain (3041 and 3042) will continue into this trial on the successful dose previously established. This dose may be titrated up or down as required. For patients entering this study without previous exposure to FEBT, a titration paradigm similar to that conducted in the pivotal efficacy trials will be performed. Visits in this study will occur monthly.

Patients:

- > N ~750 entered (100 from the efficacy studies)
- > Patients completing the pivotal studies
- > Patients with chronic noncancer pain that have at 1 to 4 BTP episodes per day
- > Average episode of BTP is 4 hours or less
- > On >60 mg/day of oral morphine or equivalent

Outcome Variables:

- > Safety
- > Global evaluation of effectiveness

- Average dose at beginning and end of treatment
- Function scale (modified Oswestry, goal-attainment scale)
- Patient preference for BTP medication
- Brief Pain Inventory Short Form
- Profile of Mood States
- SF-36

Appendix III

Primary Package Specifications and Proposed Primary Label

Primary Packaging Materials

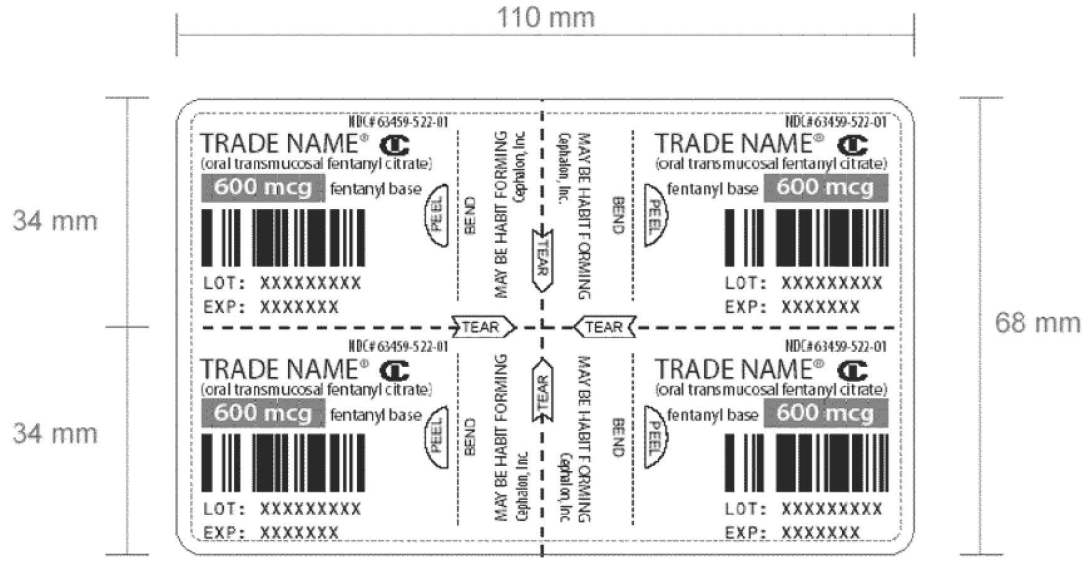
Bottom web: (Alcan 92011 and N_FP036)	
PVC Film (60 micron)	Outside
adhesive	
Polyamide Film (25 micron)	
adhesive, ink, primer	
Aluminum Foil (60 micron)	
adhesive	
PVC Film (60 micron)	Inside, product contact

Lidding Material: CR peel = Alcan 15127

Paper (30#)	**Outside**
adhesive	
Polyester Film (12 micron)	
adhesive	
Aluminum Foil (25 micron)	

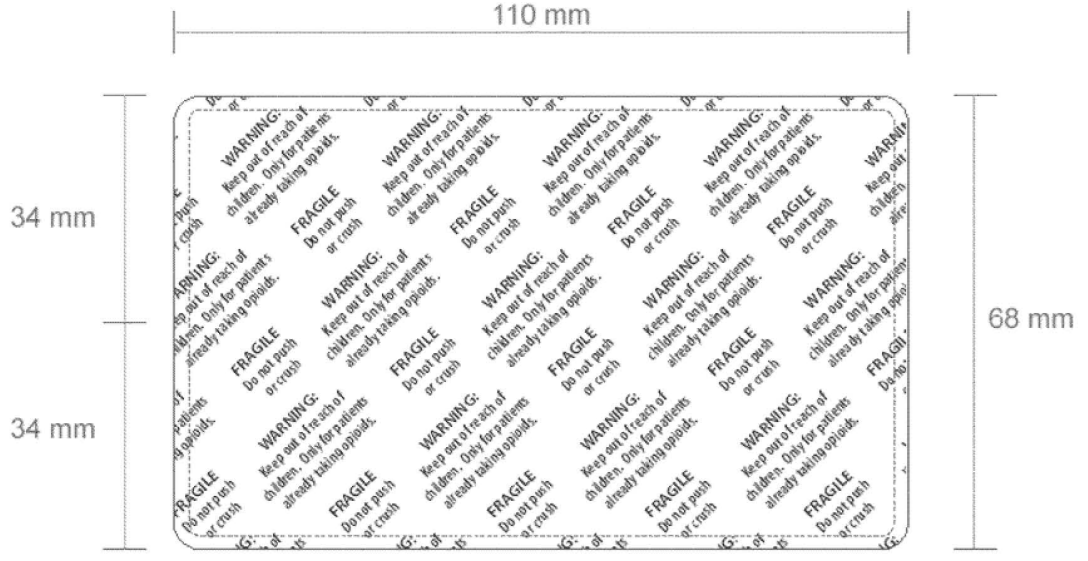
Proposed Blister Card Label

Lid Stock



Red lines do not print, text edge limits and perforation reference only

Dome Side



Red lines do not print, text edge limits and perforation reference only

Appendix IV

Glossary of Acronyms

API	active pharmaceutical ingredient
AUC	area under the drug concentration by time curve
BIO Eqi	bioequivalence
BST	Business Strategy Team
BTP-C	Break Through Pain in Cancer Patients
BTP-NC	Break Through Pain in Non Cancer Patients
C_{max}	peak plasma concentration
CR	child resistant
CRO	Contract Research Organization
CSR	clinical study report
FDA	Food & Drug Administration
FPFV	first patient first visit
HECON	Health economics
HEOR	Health economics and outcomes research
ICH	International Conference on Harmonization
IND	investigational new drug
LBP	low back pain
LPLV	last patient last visit
MD PK	multidose pharmacokinetics
NDA	new drug application
NPP	neuropathic pain
OL	Open Label

FEBT	OraVescent® Fentanyl
PBO	placebo
PCA	patient-controlled analgesia
PID	pain intensity difference
PK	pharmacokinetics
PR	Pain relief
P&RE	Pricing and reimbursement
RE	Reimbursement
RMP	Risk Management Program
SLC	Salt Lake City
sNDA	supplemental new drug application
SPID	sum of pain intensity difference
Ss	Steady state
t_{max}	time to reach peak plasma concentration

Appendix 4 Risk MAP

Background

Rationale for the RiskMAP

Fentanyl citrate has been marketed in the United States for more than 30 years, and the drug has a long record of safe and effective use when utilized as directed in the treatment of pain. Presently, fentanyl is marketed in the U.S. in a variety of formulations including those for intravenous or intramuscular administration as well as those intended for transdermal or oral transmucosal delivery.

TRADE NAME (fentanyl effervescent buccal tablets), a potent rapid-onset opioid analgesic with effects similar to morphine, has been evaluated in clinical trials at strengths of 100, 200, 400, 600, and 800 mcg for the treatment of breakthrough pain in patients with cancer who are tolerant to opioid therapy. Currently the only other drug marketed for the management of breakthrough pain in patients with cancer is ACTIQ®, a formulation of fentanyl citrate which is a lozenge dosage form on a handle. Like ACTIQ, TRADE NAME will be listed under the Controlled Substances Act as a CII product and labeling for the product will contain a boxed warning.

As noted by Food and Drug Administration (FDA) in its RiskMAP Guidance (2005), opiate drug products have important benefits in alleviating pain but are associated with significant risks of overdose, abuse, and addiction. FDA recommends that sponsors of Schedule II controlled substances consider developing RiskMAPs for these products. Because TRADE NAME contains a potent opiate, fentanyl, this RiskMAP is focused on minimizing three risks:

(1) Use of TRADE NAME by opioid non-tolerant individuals;

(2) Misuse, abuse and diversion of TRADE NAME; and;

(3) Unintended (accidental) exposure to TRADE NAME.

For each of these risks, a series of goals and accompanying measurable objectives have been established. In the implementation of the RiskMAP, tools will be employed to mitigate each of the risks. The overarching goal of this RiskMAP is to minimize specific risks associated with TRADE NAME while preserving the product's benefits.

Risks to be Minimized

Risk 1: Use of TRADE NAME by opioid non-tolerant individuals

As is the case with the use of all opioids, individuals using fentanyl citrate who are not tolerant to opioids are at risk for clinically significant and life-threatening adverse events such as respiratory depression. The risk is present at any dose in such individuals and the risk increases with dose. Therefore, TRADE NAME must not be used by opioid non-tolerant individuals as the safety and effectiveness of TRADE NAME in this population has not been established. Patients considered opioid-tolerant are those who are taking at least 60 mg of oral morphine per day, 25 mcg of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, or an

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

equianalgesic dose of another opioid for a week or longer. By limiting the use of TRADE NAME to those already taking opioid products for a sufficient time frame at sufficient levels, the risk of serious outcomes such as respiratory depression may be minimized.

TRADE NAME will likely be used primarily in the outpatient setting. To assure that at-risk patients are identified and that TRADE NAME is used only in opioid tolerant patients, Cephalon is initiating a risk-minimization program that contains multiple channels of communication and mutually reinforcing educational messages targeted toward physicians who prescribe TRADE NAME, pharmacists who dispense TRADE NAME, as well as toward the patients themselves.

Risk 2: Misuse, abuse and diversion of TRADE NAME

The abuse liability of opioids is well known and has been characterized in the medical and lay literature as well as in the media. Opioid misuse and abuse have been known to be a precursor to addiction. The actual rate of addiction to opioids is not known, but has been estimated to be between 4-10% (Savage 1996).

TRADE NAME is an effective opioid analgesic that delivers pharmacologically significant amounts of fentanyl to the brain. Fentanyl is a known drug of abuse, and the TRADE NAME dosage form (effervescent buccal tablets) has the potential to be abused. Consequently, TRADE NAME will be labeled, regulated, and listed as a Schedule II opioid, as are all other fentanyl products.

The pharmacokinetic and pharmacodynamic profile of a drug can influence its abuse liability. These are not fixed characteristics of the drug itself, but are affected by the dosage form and route by which the drug is delivered. The pharmacokinetic time course of effervescent buccal tablets is slower with lower peaks than comparable doses of injected fentanyl, and this suggests a reduced abuse liability for buccally administered TRADE NAME.

The abuse liability of a product is based on a complex interplay of many factors which include drug characteristics, patient characteristics, as well as societal and other influences. Among these many factors, rapid onset of action is a drug characteristic that may contribute to increased abuse liability. This view is supported by the evidence of attempts to reconstitute long-acting opioids into formulations with a rapid onset of action (eg, crushing Oxycontin tablets, withdrawing fentanyl from a patch for use in a syringe).

Though cases of abuse have been reported for ACTIQ, a product with a relatively fast onset of action, widespread abuse has not been identified.

Opioids, such as Oxycontin, have experienced 'geographic hot spots' and regional differences in abuse rates, where there is significantly more abuse or misuse and/or diversion than in most other geographic areas. Exact rates of diversion are not known, but diversion is known to have occurred as a result of pharmacy theft/loss, fraudulent prescriptions, individuals obtaining the medication from physicians under false pretenses, patients selling or otherwise diverting drugs, wholesaler loss, manufacturer loss, leftover product not being destroyed, and other factors.

In designing this RiskMAP, Cephalon has focused on ensuring the integrity of its supply chain for TRADE NAME, has identified tools that can be used to educate broadly, and is attempting to identify mechanisms by which cases of diversion or abuse as well as geographic incidents can be detected promptly.

Risk 3: Unintended (accidental) exposure to TRADE NAME

The risk of serious consequences from accidental exposure to TRADE NAME is greater in individuals not-tolerant to opioids. Therefore, the risk of unintended exposure to the drug can be viewed as a component of the first risk described above (use of TRADE NAME by opioid non-tolerant individuals). And while the tablet formulation and packaging of TRADE NAME is not expected to be intrinsically more interesting or appealing to children than tablet formulations in blister packs of other drugs, the epidemiology of accidental ingestions (which as described below occur primarily in the pediatric age group) and the risk of serious consequences from accidental exposure to TRADE NAME make the risk of unintended exposure to the product one that should be addressed in this RiskMAP.

Epidemiology of Unintended Poisonings

The literature on unintended poisonings in the United States indicates that children are at highest risk for accidental ingestion. Of 2.4 million poisonings reported to American Association of Poison Control Centers-Toxic Exposure Surveillance System (AAPCC-TESS) in calendar year 2003, 52% occurred in children aged less than 6 years. Epidemiologic data indicate that the peak incidence of accidental child poisoning is at 15 - 17 months of age, declining rapidly between ages 3 years through 6 years. This observed peak in poisoning incidence coincides with the period of increasing mobility of toddlers and resulting exploration of the environment that is commonly associated with oral exploratory (hand-to-mouth) behavior.

More than half of poison center contacts are due to the exposure of toxic substances to children less than 6 years of age. This same population comprises 3.1% of fatalities (AAPCC-TESS, 2003). This observation suggests that even though childhood exposures are common, the substances most commonly ingested by young children (eg, cosmetics, household cleaners, and plants) are usually of relatively low inherent toxicity. Similarly, fatalities as a result of pharmaceutical ingestions are observed in a similar manner, ie, in calendar year 2003, a total of 20 fatal pharmaceutical ingestions in children aged less than 6 years occurred; four fatal pharmaceutical ingestions in children aged 6 years - 12 years were reported.

There is considerable literature on the prevention of childhood poisoning. It has been documented that a substantial proportion of childhood poisonings can be prevented by keeping medications in child-resistant containers. In contrast, poison warning labels designed for children do not appear to be effective. Additionally, the ability of aversive bittering agents has not been proven to reduce the incidence or severity of childhood poisoning.

Implications of Poisoning Epidemiology for TRADE NAME

The efficacy and safety of TRADE NAME dosage strengths have been studied in the treatment of breakthrough pain only in adult opioid-tolerant patients. To date there are no data regarding the safety or efficacy of TRADE NAME in children. Given the known pharmacology of TRADE NAME, its rapid onset of action, and the dosage strengths available (up to 800 mcg of fentanyl), it can be anticipated that if a child who is not tolerant to opioids inadvertently is exposed to TRADE NAME, even in single unit doses, ingestion could result in significant toxicity or death.

Based on the epidemiological data cited above, it appears that the risk of accidental childhood poisoning involving TRADE NAME can be reduced through a number of mechanisms including child-resistant packaging and safety reminders (including instructions for proper storage, use, and disposal of medications), which remain the mainstay of poisoning prevention in young children. Cephalon will be using F1 packaging for TRADE NAME, which is the most stringent of child-resistant packaging requirements (see Glossary).

In addition, physicians who prescribe TRADE NAME can assess whether children are ever in the home of a patient. Directed counseling of these patients and those with children can be initiated and reinforced by healthcare professionals, including physicians, pharmacists and nurses, involved in the patient's care. These healthcare professionals can reinforce with the patient the need to prevent children's access to TRADE NAME. Patients themselves can be educated on the risk that TRADE NAME poses to children and can be given guidance on storage and disposal of the medication.

Although adults are less likely to experience unintended exposure to TRADE NAME than children, this RiskMAP also considered accidental exposure that could occur in adults, such as a result of cognitive impairment or due to medication errors. Steps could be taken to minimize such risks as well. For example, when prescribing TRADE NAME, physicians can assess the ability of their patients to self-administer the medication as directed. When this ability is in question, the patient's caregivers can be counseled by healthcare professionals with guidance similar to that given above to those with children in the home. Product distinctions in packaging, labeling, and the physical appearance of TRADE NAME are all factors that can contribute to decreasing the risk of medication errors which could be caused by inadvertent substitution of another medication for TRADE NAME.

In conclusion, as part of this RiskMAP, Cephalon is implementing interventions beyond product labeling specifically to target unintended TRADE NAME exposures (see section 0).

Risk-Benefit

Potential Benefits

Breakthrough pain (BTP) in patients with cancer is a well-recognized entity, and it is important that the pain be managed adequately as part of an overall pain management program for a patient. Because of the prevalence and inherent consequences of BTP, it is recommended that patients with chronic pain on regular opioid treatment regimen be

provided with supplemental opioid medications for the management of BTP (American Pain Society, 2003). For patients taking around-the-clock opioid therapy, the most commonly used medications for BTP are immediate-release oral opioids. It has been noted, however, that these medications are likely to be inadequate for a substantial proportion of patients (Portenoy et al 1999) because these medications typically take about 30 minutes to begin producing analgesic effects, whereas the onset of peak pain intensity of BTP for most patients occurs within just a few minutes.

As was shown in the pivotal randomized, double-blind, placebo-controlled efficacy study of cancer patients with breakthrough pain, TRADE NAME results in rapid onset of analgesia with extensive absorption and a lasting, even improving effect. The efficacy results showed that effervescent fentanyl had analgesic effects 15 minutes after tablet placement (the earliest time point assessed) and maintained superiority in analgesic effect compared with placebo treatment through the 60-minute observation period as evidenced by changes in pain intensity and pain relief scores. In addition, patients were twice as likely to require supplemental opioid analgesics for BTP episodes for which placebo was used than for those episodes for which effervescent fentanyl was used. The superiority of effervescent fentanyl to placebo treatment was demonstrated by all measures of efficacy (pain intensity, pain relief, global medication performance, and use of supplemental rescue medication) and at all time points (15, 30, 45, and 60 minutes after treatment). The effects were both statistically significant and clinically relevant.

While fentanyl has long been recognized as a potent analgesic, there are inherent advantages to the buccal tablet formulation of effervescent fentanyl. Fentanyl effervescent buccal tablets are uniquely formulated with effervescence ingredients and pH adjusters to facilitate a rapid and extensive absorption of fentanyl through the oral mucosa. Its observed pharmacokinetic profile indicates that approximately 50% of effervescent fentanyl is rapidly absorbed and quickly becomes systemically available. These formulation and pharmacokinetic characteristics mean that lower doses are needed by patients for attainment of therapeutically effective plasma concentrations than those required with ACTIQ, a fentanyl lozenge on a handle (solid dosage form). Specifically, this rapid absorption results in peak plasma concentrations being reached nearly twice as fast as ACTIQ, allowing for therapeutically effective plasma concentrations to be achieved earlier. These product qualities are advantageous for a condition such as BTP when the time from onset to maximum intensity is short. Because the effervescent formulation is a more efficient delivery system, the tablet strengths of effervescent fentanyl (100 to 800 mcg) are lower than the unit strengths of ACTIQ (200 to 1600 mcg).

Unlike administration of ACTIQ, a transmucosal fentanyl lozenge on a handle, administration of a buccal tablet is not only less patient dependent but is also more discreet and convenient for the patient. The simplicity of administration of a tablet potentially allows for more consistent delivery of fentanyl because it is less patient dependent (ie, a passive delivery system is less prone to patient error than an active delivery system).

Potential Risks

While TRADE NAME has been shown to benefit opioid-tolerant patients with breakthrough cancer pain, the product also has side effects and risks.

Because effervescent fentanyl is a potent opioid analgesic, it may produce side effects similar to those seen with other products of its class. In addition, the transmucosal route of delivery for effervescent fentanyl could lead to risk of oral mucosal irritation. On the basis of experience from clinical studies, about 8% of patients treated with effervescent fentanyl had adverse event that could be considered related to tablet application site (eg, application site pain, ulcer, or burning). In general, these adverse events were not serious and did not lead to stopping treatment. Additionally, opioid analgesics may impair mental and/or physical ability required for the performance of potentially dangerous tasks such as driving a car or operating machinery

As described above, because it is a potent μ-receptor agonist, there are inherent risks with effervescent fentanyl to populations for which the product is not intended, particularly people who are not opioid tolerant. One such risk is that of respiratory depression, although this side effect was not seen in clinical studies with effervescent fentanyl.

Like other drugs of its class, effervescent fentanyl may be habit forming or potentially abused, and as such, physicians should use caution when prescribing it to patients. 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 mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed effervescent fentanyl. All patients receiving effervescent fentanyl should be routinely monitored for signs of misuse, abuse, and addiction.

During clinical studies of effervescent fentanyl, there were no reports of patients abusing effervescent fentanyl or patients who experienced an overdose. Two patients in study 15 were withdrawn from the study at the request of the sponsor due to the theft of tablets of effervescent fentanyl from these patients' homes. In both cases, the patients had family members with a history of drug abuse, and there were questions about whether the family members were involved in the theft.

As with other fentanyl formulations (the transdermal patch or ACTIQ), the potential exists for abusers to extract fentanyl from effervescent fentanyl tablets. The efficiency of the effervescent delivery system enables similar plasma levels of fentanyl to be obtained with doses of fentanyl that are lower than those required with ACTIQ. The tablet strengths for effervescent fentanyl (100, 200, 400, 600, and 800 mcg) are half those of the available dose strengths for ACTIQ (200, 400, 600, 800, 1200, and 1600 mcg). Moreover, the amount of fentanyl in the effervescent tablets is also substantially lower than the 10 mg of fentanyl present in the 100-mcg/h transdermal patch. Although the risk of extraction is present for effervescent fentanyl, the amount of drug available is lower than with these other formulations.

Manipulation (eg, crushing) of the effervescent fentanyl tablets is not likely to substantially alter the absorption characteristics of the medication when administered buccaly or orally. Although intranasal and intravenous administration of a crushed tablet is possible, the risk of occurrence is not considered to be any greater than for other strong μ-opioids (eg, oxycodone, hydromorphone, or morphine).

There is also a risk of unintended exposure to TRADE NAME. The tablet formulation of TRADE NAME and its packaging is not expected to be intrinsically more interesting or appealing to children than tablet formulations and packaging of other drugs. But the epidemiology of accidental ingestions indicate that they occur primarily in the pediatric age group, and there is a risk of serious or fatal-consequences from accidental exposure to TRADE NAME, particularly in individuals not opioid tolerant.

Cephalon has developed a RiskMAP to mitigate three of the risks identified above: (a) use by opioid non-tolerant individuals; (b) misuse, abuse, and diversion; and (c) unintended (accidental) exposure to the medication.

The overall goal of this RiskMAP is to minimize the risks of TRADE NAME while preserving its important medical benefits.

RiskMAP Goals and Objectives

For purposes of this RiskMAP, Cephalon uses the term "goals" and "objectives" in a manner consistent with FDA's Guidance for Industry: Development and Use of Risk Minimization Action Plans (2005). These definitions emphasize that whereas goals are absolute and ideal, objectives are pragmatic and measurable (Section III.C of the guidance):

> *FDA suggests that sponsors state goals in a way that aims to achieve maximum risk reduction. The following are examples of RiskMAP goals: "patients on X drug should not also be prescribed Y drug" or "fetal exposures to Z drug should not occur." FDA recommends that goals be stated in absolute terms. Although it might not be possible to ensure that absolutely no one on X drug receives Y drug, FDA believes that a goal as the term implies is a statement of the ideal outcome of the RiskMAP.*
>
> *FDA recommends that RiskMAP goals be translated into pragmatic, specific and measurable program objectives that result in processes or behaviors leading to achievement of the RiskMAP goals Objectives can be thought of as intermediate steps to achieving the overall RiskMAP goal. A RiskMAP goal can be translated into different objectives, depending upon the frequency, type, and severity of the specific risk or risks being minimized. For example, a goal may be the elimination of dangerous concomitant prescribing. The objectives could include lowering physician co-prescribing rates and/or pharmacist co-dispensing rates.*

Cephalon has identified three goals that express the ideal outcome of the TRADE NAME RiskMAP. These goals are based on the risks identified in section 0 (Risks to be Minimized). With each of these goals, there are specific and measurable program objectives that are described below.

Goals

(1) Goal 1: TRADE NAME should be used only by opioid tolerant individuals.
(2) Goal 2: Abuse, Misuse and Diversion of TRADE NAME should not occur.
(3) Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur.

Objectives

Goal 1: TRADE NAME should be used only by opioid tolerant individuals

Objectives:

i. To educate practitioners that TRADE NAME should not be used in opioid non-tolerant patients
ii. To ensure patients understand that TRADE NAME should be used only by individuals who are opioid tolerant

iii. To educate prescribers and other healthcare personnel (eg, pharmacists and nurses) so that they are aware of the importance of TRADE NAME being prescribed, distributed, and administered only to opioid tolerant patients.

Goal 2: Abuse, Misuse and Diversion of TRADE NAME should not occur

Objectives:

i. To ensure adequate controls are instituted, evaluated, and maintained to prevent the diversion of TRADE NAME from Cephalon's supply chain.

ii. To ensure adequate education, surveillance, and interventions are instituted and maintained to minimize diversion of TRADE NAME when the product is no longer within Cephalon's supply chain.

iii. To reduce the potential abuse, misuse, and diversion of TRADE NAME by (a) providing education to healthcare personnel and to pertinent nationwide demographic communities; (b) performing ongoing surveillance of abuse, misuse, and diversion; and, (c) cooperating with and providing assistance to law enforcement in investigations of incidents of abuse or diversion.

Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

Objectives:

i. To reduce or eliminate accidental exposure through product packaging which has been designed and tested so as to reduce or eliminate unintended access to TRADE NAME by at-risk populations.

ii. To reduce or eliminate accidental exposure by properly educating patients about "safe product use" at the point of prescribing and dispensing.

iii. To reduce or eliminate departures from "safe product use" at the time of actual or intended use of TRADE NAME.

iv. To reduce or eliminate accidental exposure during storage of TRADE NAME and to ensure that mechanisms exist to facilitate the prompt return and/or disposal of all unused TRADE NAME when it is no longer needed.

Strategy and Tools

Overall Strategy

Cephalon developed the RiskMAP for TRADE NAME with specific reference to FDA and International Conference on Harmonisation (ICH) Guidances entitled *"Guidance for Industry: Development and Use of Risk Minimization Action Plans"* and *"Quality Risk Management Q9."* In the development of the RiskMAP, Cephalon also called on its extensive knowledge and experience with implementing its Risk Management Program for ACTIQ, a closely related product. In addition, principles and methodology of other risk assessment tools, such as Failure Mode Effects Analysis (FMEA), were used to evaluate the potential risks associated with use of TRADE NAME.

Failure Mode Effects Analysis (FMEA) is a systematic, prospective risk-analysis process. Prospective risk management activities allow pharmaceutical companies to minimize the occurrence of errors, whereas a retrospective activity, such as root-cause analysis, analyzes errors after they have occurred. An objective of Cephalon's application of some of the principles and methodology of FMEA is to minimize the occurrence of the identified risks by scrutinizing the identified system processes. FMEA employs the following six steps:

(1) Choose a process for investigation.
(2) Form a multidisciplinary team.
(3) Map out the process, including each step.
(4) Calculate a risk priority for each step in the process.
(5) Select an area for improvement based on the calculated risk priority.
(6) Implement actions and outcome measures.

A multidisciplinary team was assembled, which was comprised of representatives with expertise from several different areas, including medical, legal, regulatory, commercial, and scientific affairs, with the purpose of identifying anticipated risks that could occur with the commercialization of TRADE NAME. The team identified 3 principal risks which have been described above (see section 0: Risks to be Minimized). The team then analyzed the points of intervention where undesirable incidents could occur, beginning with the initial steps in commercialization of the product and ending with the disposal of the product. The six points of intervention identified were the following:

(1) supply chain;
(2) point of prescribing;
(3) point of dispensing;
(4) consumer storage;
(5) patient use (also referred to as consumer use); and,
(6) disposal of product.

The team then considered tools that are currently available, those which are familiar to Cephalon through its ACTIQ Risk Management Program, and those identified through

consultation with outside experts. Subsequently, each risk was assessed to determine the potential success of the tools at each of the 6 points of intervention. The points where potential failures could occur were than identified and tools were selected to minimize the risks at these points. Appendix A summarizes principal tools being employed in this RiskMAP.

Following a reasonable time after commercialization of TRADE NAME, such as when sufficient data have been accumulated to ascertain whether the key messages are being adequately communicated (eg, approximately 6-12 months), the risks associated with TRADE NAME and points of departure from the principles of the RiskMAP will be analyzed, if possible using some of the principles of FMEA. When feasible, these analyses will review each type of risk for seriousness or severity and will provide an estimate of frequency or probability of the event. An example of how a criticality index can be estimated in such an analysis is described in Table 1.

Table 1: An Example of the Application of the Criticality Index in Failure Mode and Effects Analysis

Rating	Potential Effect of Risk on Patient (Seriousness or Severity)	Frequency of Error	Likelihood of Error Reaching Patient
10	Catastrophic	Frequent	Absolute
7-9	Major	Occasional	Probable
4-6	Moderate	Uncommon	Possible
1-3	Minor	Remote	Doubtful

In formal quantitative FMEA, a criticality index can be calculated by multiplying the mean rating scores for severity/seriousness, frequency of error, and likelihood of reaching the patient. Higher scores of the criticality index represent more critical errors and can help identify the most important failures in a system and identify areas where key messages might need to be reinforced or where interventions might need to be adjusted.

Several key messages will be provided to health professionals and patients in the redundant tools throughout the RiskMAP. They will convey that TRADE NAME:

- contains fentanyl citrate,
- is a Schedule II opioid,
- should be used by opioid-tolerant patients (defined by the package insert) because of the risk of serious outcomes such as respiratory depression
- has a risk of misuse, abuse, and diversion
- should be kept out of the reach of children,
- is indicated for breakthrough pain in patients with cancer, and

- is contraindicated in acute pain or post-operative pain.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of each of these messages and their implications.

Strategy and Tools Associated with Goal 1: TRADE NAME should be used only by opioid-tolerant individuals

A variety of tools will be used to communicate and reinforce the message that TRADE NAME should be used only by opioid-tolerant individuals. The tools selected have been chosen for specific purposes and are intended for three specific primary audiences: prescribers, pharmacists, and patients.

From the outset, healthcare professionals such as physicians and pharmacists will be alerted to the risks of this new product, will be provided product labeling, and will be educated about the product's approved indication as well as about the definition of "opioid-tolerant" as described in the package insert. Inclusion of the risk information in the label will assure consistency of the risk warning in a variety of media including all promotional materials.

Tools directed toward prescribers will include, but are not limited to, introductory letters, visits and assessments by Cephalon field representatives, educational monographs, and targeted education and outreach programs directed to Pain Centers of Excellence and professional societies.

Tools directed toward pharmacists also will include introductory letters (PharmAlert) and visits by Cephalon field representatives. In addition, counseling messages will be distributed to pharmacies by major publishers of pharmacy counseling software. A reminder checklist is printed on the carton to prompt the pharmacist at the point of dispensing to make sure the patient is opioid tolerant before dispensing TRADE NAME and to encourage the patient to read the TRADE NAME Medication Guide.

The Medication Guide describes for the patient, in understandable non-technical language, the serious risks associated with effervescent fentanyl tablets. It provides information necessary for the patient to use the product safely and effectively. Patients will also benefit from the use of written counseling aids provided by Cephalon to physicians and pharmacists. These aids will encourage an open dialogue about TRADE NAME between the healthcare professional and the patient, thereby encouraging active participation of the patient in his/her medical care.

Table 2 summarizes the interventions that will be employed to minimize the risk of TRADE NAME being used by opioid non-tolerant individuals. It describes each of the tools and the audiences applicable to each of the interventions.

The surveillance and monitoring activities associated with the proactive interventions described above is located in section 0 and Table 5.

Table 2: Goal 1 Summary Table

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Patient Use	Patients	Targeted Education & Outreach	Blister label	Launch and Ongoing: The blister label (dome side) will contain important warning information ("Only for patients already taking opioids")
1	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains important warning information ("Only for patients already taking opioids such as fentanyl or morphine;" and "TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed TRADE NAME."). A reminder checklist is printed on the carton to prompt the pharmacist to advise the patient that TRADE NAME should be used only by opioid tolerant individuals and to encourage the patient to read the Medication Guide. The carton label directs the patient and/or caregiver to read the enclosed Medication Guide for important warnings.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide will emphasize the need for the patient to be opioid-tolerant. It will warn the patient of the potentially serious consequences, including death, of using TRADE NAME if not opioid tolerant. It will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of TRADE NAME in opioid non-tolerant individuals. It will define opioid tolerance.
1	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use of TRADE NAME by an individual not tolerant to opioids.
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce the use of TRADE NAME only by opioid-tolerant individuals. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and 3,000 pharmacists likely to stock TRADE NAME, the top 25 Pain Centers of Excellence.
1	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce the use of TRADE NAME only by opioid-tolerant individuals. The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence.
1	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that reinforces the use of TRADE NAME only in opioid-tolerant individuals will be distributed to 40,000 retail pharmacists.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the risks of use by opioid non-tolerant individuals. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the TRADE NAME RiskMAP.
1	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks associated with the use of TRADE NAME, including the risk of its use by opioid non-tolerant individuals.
1	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Counseling aids	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the risk and potentially life-threatening consequences of use of TRADE NAME by individuals not tolerant to opioids.
1	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the risk of the use of TRADE NAME by opioid non-tolerant individuals. The educational platform for these offerings will include symposia at the professional society's meeting(s) and/or teleconferences with interested members.

(continued)

Table 2: Goal 1 Summary Table (Continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tools**	**Description**
1	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about its use in opioid non-tolerant individuals) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.
1	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use of TRADE NAME by individuals not tolerant to opioids. The pharmacists will be alerted to the utility of the Medication Guide
1	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that TRADE NAME should be used only by opioid-tolerant patients.
1	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of use in opioid non-tolerant patients will be reviewed. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the risk associated with use of TRADE NAME in opioid non-tolerant patients. Evaluations will be provided to verify that the speakers presented the required risk information.

Table 2: Goal 1 Summary Table (continued)

Goal 1: TRADE NAME should be used only by opioid-tolerant individuals					
Goal	**Point(s) of Intervention**	**Primary Audience(s)**	**Tool Category**	**Tool**	**Description**
1	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP and the use of TRADE NAME in opioid non-tolerant patients. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the TRADE NAME RiskMAP.

Strategy and Tools Associated with Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur

The risks of misuse, abuse and diversion are inherent with CII opioid drugs. To successfully address this risk in an environment where prescription drug abuse rates have been growing over the past several years requires a combination of efforts including supply chain integrity activities, educational interventions, and ongoing surveillance and monitoring activities. Law enforcement agencies also play a significant role in limiting illicit activities associated with abuse and diversion. Healthcare professionals (eg, physicians, pharmacists, nurses) who deal with Schedule II opiates should be versed in Federal, state, and local legal and regulatory requirements governing their use.

The listing of TRADE NAME under Schedule II of the Controlled Substance Act is one of the principal tools that will aid in limiting the degree to which the medication is abused and diverted. Federal and state laws and regulations govern the manufacturing, distribution, prescribing, dispensing, storage, and disposal of CII products, and there are extensive controls, record keeping requirements, and auditing functions in place to minimize the risk of abuse and diversion. For example, prescriptions for CII products must be written in ink, or typewritten and signed by the practitioner. Verbal prescriptions must be confirmed in writing within 72 hours, and may be given only in a genuine emergency. No renewals are permitted.

In evaluating the tools to reduce the risk of misuse, abuse and diversion associated with the use of TRADE NAME, Cephalon identified several points of intervention in the product's safe-product-use pathway (see Glossary). The early part of this supply chain is most directly under Cephalon's control because of the Company's internal standard operating procedures (SOPs) and auditing capabilities. Controls are applied from the time Cephalon is in receipt of fentanyl citrate throughout the manufacturing and packaging of the finished product, and through distribution to wholesalers.

To help minimize the risk of diversion of TRADE NAME, Cephalon will track every shipment of TRADE NAME 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 from Cephalon to when it is received by the wholesaler. Wholesalers who purchase product from Cephalon will be alerted to the goals of the TRADE NAME RiskMAP, and the wholesalers will verify that they have processes and procedures in place to minimize the risk of diversion when the product is received by the pharmacies.

Given the control Cephalon has over its supply chain, opportunities for departures from the safe-use pathway are likely to increase for TRADE NAME after it leaves the Cephalon supply chain. This suggests the need for additional efforts at the following points of intervention: point of prescribing, dispensing, patient use, and disposal of the product.

At the point of prescribing, physicians should use caution when prescribing TRADE NAME to patients and should be aware of circumstances, symptoms, and signs that could contribute to an individual's risk of abuse. 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 mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed effervescent fentanyl. All patients receiving effervescent fentanyl should be routinely monitored for signs of misuse, abuse, and addiction. Physicians should also be familiar with methods used by individuals to obtain schedule II opiates illicitly (eg, doctor shopping, feigning illness or pain). For any given patient, physicians considering the use of TRADE NAME should balance the risks of product misuse, abuse, and diversion with the important medical need to adequately treat pain.

Similarly, at the point of dispensing, pharmacists should also exercise caution when dispensing TRADE NAME to patients. Pharmacists, too, should have familiarity with factors that could contribute to an individual's risk of abuse, and should be knowledgeable about methods used by individuals to obtain schedule II opiates illicitly (eg, fraudulent prescriptions, pharmacy theft).

Patients should be aware that TRADE NAME contains a schedule II opioid pain medication and that they may become addicted to this class of medications. They should be counseled that their risk for abuse and addiction may be higher if they have a history of abuse of other medications, street drugs, or alcohol, or if they have a history of mental illness. Patients should also be counseled that TRADE NAME contains a federally controlled substance and that to sell or give their medication to others is a violation of the law. Patients should also be advised that they could become targets for those who abuse prescription medications or street drugs, and that they should always store TRADE NAME in a safe place.

Tools will be employed at each of these points of intervention to minimize the risk of abuse and diversion. To inform physicians of these risks, for example, TRADE NAME monographs will be distributed and educational programs will be targeted to members of professional societies. Another example of a tool designed to aid the pharmacist as well as other healthcare professionals in this area is the use of well-known pharmaceutical compendia which will highlight the high abuse potential of TRADE NAME. The PharmAlert system will be used to target education and outreach efforts to pharmacists. The Medication Guide is an example of a tool intended for patients that conveys important information about misuse, abuse, and diversion in non-technical, scientifically accurate language.

Surveillance and monitoring activities for abuse and diversion will be discussed in section 0 and Table 5.

Table 3 provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of misuse, abuse, and diversion of TRADE NAME

Table 3: Goal 2 Summary Table

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Dispensing Patient Use	Patients Pharmacists	Targeted Education & Outreach; Reminder system	Carton label	Launch and ongoing: The labeling of the carton contains several items of information intended to decrease misuse of the product (eg, "For Buccal Administration. Do not Swallow Tablet"). In addition the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to counsel the patient about the use of TRADE NAME and to encourage the patient to read the TRADE NAME Medication Guide (which provides important warnings and directions). Similarly, the CII scheduling status of TRADE NAME is noted prominently on the carton to remind the pharmacist that TRADE NAME has a high potential for abuse.
2	Prescribing Dispensing Patient Use	Patients Pharmacists Prescribers	Targeted Education & Outreach	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide provides information to the patient intended to minimize misuse, abuse, and diversion. It includes, for example, a section titled "How should I take "TRADE NAME." which provides instructions on proper administration of the buccal tablet. As for abuse, it warns that the patient may become physically dependent on opioids and could become addicted to TRADE NAME. For diversion, it warns patients that TRADE NAME is a federally controlled substance, that selling the medication or giving it away is against the law, and that the medication should be kept in a safe place to protect it from being stolen. The Medication Guide will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.

(continued)

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing. The package insert will contain information about opioid misuse, abuse, diversion, and addiction and can serve as a useful reference to healthcare professionals.
2	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including information on the high potential for TRADE NAME abuse as well as of its risk of misuse and diversion.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce key messages of the RiskMAP including the risk for TRADE NAME misuse, abuse, and diversion. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME, 3,000 retail pharmacists likely to stock TRADE NAME, and the top 25 Pain Centers of Excellence.
2	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce messages about the risk of misuse, abuse, and diversion of TRADE NAME The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence
2	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that reinforces the use of TRADE NAME is associated with a risk of misuse, abuse, and diversion. This material will be distributed to 40,000 retail pharmacists.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including its risks for misuse, abuse, and diversion. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the TRADE NAME RiskMAP.

(continued)

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the risks for misuse, abuse, and diversion.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Education materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that the use of TRADE NAME is associated with misuse, abuse and diversion.
2	Dispensing Patient Use	Pharmacists Patients	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the risks of misuse, abuse, and diversion associated with the use of TRADE NAME.
2	Prescribing	Prescribers	Targeted Education & Outreach	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the 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.
2	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about its misuse, abuse and diversion) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.

(continued)

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of misuse, abuse and diversion associated with use of TRADE NAME. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify they understand the risk of misuse, abuse and divserion associated with use of TRADE NAME. Evaluations will be provided to verify that the speakers presented the required risk information.
2	Prescribing	Prescribers and Pharmacists	Targeted Education & Outreach	Physician and Pharmacist education	Ongoing (response to surveillance): 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 the specific need (eg, symposium, teleconferences, print materials, etc.)
2	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP and the risk for misuse, abuse and diversion associated with use of TRADE NAME. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the RiskMAP.
2	Prescribing Dispensing	Prescriber Pharmacists	Targeted Education & Outreach	Independent continuing medical education (CME)	Launch: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe TRADE NAME.

Table 3: Goal 2 Summary Table (Continued)

Goal 2: Misuse, abuse and diversion of TRADE NAME should not occur					
Goal	**Point(s) of Intervention**	**Audience**	**Tool Category**	**Tools**	**Description**
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Targeted Education & Outreach	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alert them to safeguard against the potential diversion of TRADE NAME.
2	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the risks for misuse, abuse, and diversion for TRADE NAME. The pharmacists well be alerted to the utility of the Medication Guide.
2	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.
2	Prescribing Dispensing Patient Use	Drug Diversion Professionals	Active Monitoring	Reports of Diversion and Abuse	Launch and ongoing: Cephalon will attempt to implement an active monitoring system (eg, RADARS) at the time of the launch of TRADE NAME. Reports form the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on TRADE NAME.

Strategy and Tools Associated with Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

In contrast to ACTIQ, a transmucosal fentanyl lozenge on a handle, the tablet formulation and packaging of TRADE NAME is not expected to be intrinsically more interesting or appealing to children than tablet formulations in blister packaging of other drugs. Nonetheless, there is a risk of serious harm should a child (or cognitively impaired adult) be accidentally exposed to TRADE NAME. Consequently, Cephalon has defined a safe product use pathway that seeks to minimize the occurrence of unintended or accidental exposure to TRADE NAME in adults or children. It consists of explicit instructions and control measures that describe the safe use of the product at appropriate intervention points including during transit in the supply chain, at the point of prescribing, at the point of dispensing, during consumer storage and at the point of disposal of product. These instructions will be incorporated into product labeling and will be the first line of defense in the prevention of unintended TRADE NAME ingestions. Interventions will be introduced at the time of commercialization, and will be considered again once data have been accumulated to evaluate the extent of risk. Modifications to the tools employed in the RiskMAP may be made as appropriate.

Note that at the point of home storage, the TRADE NAME child-resistant packaging provides protection from departures from the safe product use pathway. Specifically, the TRADE NAME blister packaging has met the effectiveness specifications using the Child Test procedure for special packaging (16 CFR 1700.20(a)(2)) and has met performance specifications for an "F1" classification (see Glossary) (see Appendix B).

Table 3 provides a list of interventions, a description of each of the tools, and the audiences applicable to each of the interventions to minimize the risk of accidental exposure to TRADE NAME.

Surveillance and monitoring activities for unintended exposure will be discussed in section 0 and Table 5.

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Patient use	Patients	Package integrity	Blister	Launch and ongoing: Tablets will be supplied in double foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness. This tool is designed to minimize the risk of accidental exposure to TRADE NAME.
3	Patient use	Patients	Targeted Education & Outreach	Blister label	Launch and ongoing: The blister label warns that TRADE NAME is to be kept out of the reach of children. It instructs that TRADE NAME should be used immediately upon opening. These tools are designed to minimize the risk of accidental exposure to TRADE NAME.
3	Dispensing Patient use	Pharmacists Patients	Targeted Education & Outreach Reminder System	Carton label	Launch and ongoing: The carton labeling contains several items of information intended to decrease the risk of accidental exposure to TRADE NAME. It warns that TRADE NAME is to be kept out of the reach of children and that TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. In addition, the carton label advises the patient and/or caregiver to read the enclosed Medication Guide for important warnings and directions. The checklist on the carton reminds the pharmacist to encourage the patient to read the TRADE NAME Medication Guide (which provides important warnings and directions about accidental exposure)

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Medication Guide	Launch and ongoing: The TRADE NAME Medication Guide provides information to the patient intended to decrease the risk of accidental exposure to TRADE NAME. It warns that TRADE NAME is to be kept in a safe place away from children, and that accidental use by a child is a medical emergency that can result in death. In the event of accidental use by a child, the Medication Guide provides instructions for contacting a Poison Control Center or the nearest emergency room right away. The Medication Guide will be included in the TRADE NAME packaging and will also be made available to all prescribers and TRADE NAME stocking pharmacies (via 800#, a product-specific website, and Cephalon sales representatives) for education and dissemination to patients.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Package insert	Launch and ongoing: The package insert contains a Boxed Warning for healthcare professionals about the risks associated with the accidental exposure to TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	Direct risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of accidental use of TRADE NAME in children or adults. The pharmacists will be alerted to the utility of the Medication Guide
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Educational introductory letter to healthcare professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter which will reinforce key messages of the RiskMAP including the risk of accidental exposure to TRADE NAME. The letter will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME, 3,000 retail pharmacists likely to prescribe TRADE NAME, and the top 25 Pain Centers of Excellence.
3	Prescribing	Prescribers	Targeted Education & Outreach	Educational monograph for physicians	Launch: Cephalon will develop and disseminate an TRADE NAME educational monograph which will reinforce messages about the risk of accidental exposure to TRADE NAME The monograph will be disseminated by direct mail to 10,000 physicians likely to prescribe TRADE NAME and to the top 25 Pain Centers of Excellence.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Dispensing	Pharmacists	Targeted Education & Outreach	PharmAlert	Launch: Educational material that explains the risk of accidental exposure associated with the use of TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the risks of accidental exposure associated with the use of TRADE NAME. The educational platform for these offerings will include symposia and/or teleconferences and will incorporate the key messages of the RiskMAP.
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information (including risk information about the risk of accidental exposure to TRADE NAME) to well-known drug compendia such as the Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons
3	Prescribing Dispensing	Prescribers Pharmacists	Targeted Education & Outreach	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists in the risks associated with the use of TRADE NAME, including the risk of accidental exposure associated with its use.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing Patient Use	Prescribers Pharmacists Patients	Targeted Education & Outreach	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and education patients about TRADE NAME. This aid will include information about the risk and potentially life-threatening consequences associated with the accidental use of TRADE NAME.
3	Dispensing	Pharmacists	Targeted Education & Outreach	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education that accidental exposure is associated with the use of TRADE NAME.
3	Prescribing	Prescribers	Targeted Education & Outreach	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert including the key elements and messages of the RiskMAP, specifically the risk of accidental exposure to TRADE NAME. Cephalon will also provide speakers with information, which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify they understand the risk of accidental exposure associated with the use of TRADE NAME. Evaluations will be provided to verify that the speakers presented the required risk information.

(continued)

Table 4: Goal 3: Unintended (accidental) exposure to TRADE NAME should not occur (Continued)

Goal	Point(s) of Intervention	Primary Audience(s)	Tool Category	Tools	Description
3	Prescribing Dispensing	Cephalon field representatives	Targeted Education & Outreach	Training for Cephalon field representatives training	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP. Upon completion of training, field representatives will be tested on the training and will be required to verify they understand the information included in the TRADE NAME RiskMAP.
3	Patient Use	Patients	Targeted Education & Outreach	Product returns and Disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.
3	Patient Use	Patients	Targeted Education & Outreach	Toll-free number	Launch and ongoing: Poison control number for accidental ingestion.

Measuring Effectiveness of The RiskMAP

The RiskMAP is designed to address three principal risks associated with TRADE NAME: 1) its use by opioid non-tolerant individuals, (2) the risk of misuse, abuse, and diversion, and 3) unintended (accidental) exposure to the product. The effectiveness of the tools identified in this RiskMAP will be evaluated on an ongoing basis.

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of these risks and are aware of steps they can take to minimize them. Cephalon will employ a series of independent and unique surveillance and monitoring techniques targeted at prescribers, pharmacists, and patients, respectively, to assess the effectiveness of the targeted education and reminder systems at the points of intervention. The surveillance and monitoring activities associated with the TRADE NAME RiskMAP may be found in Table 5.

Active and Passive Surveillance Systems

Reports of spontaneous adverse events are valuable since they provide an understanding of behaviors associated with the use of a product in actual use. Databases such as TESS and DAWN and monitoring of publications will be utilized to augment Cephalon's pharmacovigilance system. Data obtained from passive reporting systems, however, may be biased toward capturing certain outcomes or can result in delays in signal detection. True rates cannot be accurately ascertained from such systems. However, Cephalon is considering employing an active surveillance system (similar or the same as RADARS) to identify the use patterns of the product to compensate for the limitations of spontaneous adverse event reporting (see section 0 and Table 2).

Surveys

Another surveillance tool utilized in the TRADE NAME RiskMAP will be the use of three separate survey systems targeted at the three principal intended audiences: prescribers, pharmacists and patients. As with any methodology, there are a number of potential limitations to use of surveys. However, a well-designed survey using appropriate controls to minimize bias could help compensate for the limitations associated with this methodology, enabling one to capture valuable measurements for assessment.

Physician Surveys

Surveys of physicians will be employed to evaluate prescribing patterns. Whereas several databases provide broad descriptive data, databases such as the NCI and IMS databases have inherent limitations in being able to evaluate physician prescribing patterns. For instance, the data are limited in that one cannot obtain the reason why a drug has been prescribed. For example, this could limit the ability to evaluate whether the practitioner is prescribing TRADE NAME to opioid tolerant patients. Surveys provide detailed information providing insight into data captured by such databases.

To provide more specific evaluative information, a sample of physicians will be selected for surveying: This survey(s) will include assessments in the following areas:

- their knowledge of the key risks associated with the use of TRADE NAME,

- their knowledge of the indication for TRADE NAME,
- their patterns of TRADE NAME prescribing (eg, opioid tolerant vs. opioid non-tolerant),
- their assessment of the risk minimization tools (eg, use of, and reaction to, various Cephalon communications),

The physician survey(s) will serve to monitor physicians' knowledge of and use of TRADE NAME. It will also monitor the awareness of prescribers to the risks associated with the use of the product in patients not-tolerant to opioids. Responses to these questions and others will be important to help understand whether adjustments in interventions or key messages will be needed to improve the RiskMAP over time.

The physician survey(s) will be repeated every six months for the first two years of the program, at which time internal and external experts associated with Cephalon will evaluate the results. Following review of the survey(s), questions and time frames may be modified.

Pharmacy Surveys

A survey targeting the dispensing pharmacists will also be employed. This survey will include assessments in the following areas:

- their knowledge of the key risks associated with the use TRADE NAME,
- their knowledge of the indication for TRADE NAME,
- their awareness and use of the carton checklist, Medication Guide, and other information about the product made available by Cephalon field representatives, and
- their assessment of the value of counseling messages provided by major publishers of pharmacy counseling software.

Patient Surveys

Finally, a patient survey will be employed to evaluate the RiskMAP tools. This survey will include assessments in the following areas:

- their knowledge of the key risks associated with the use TRADE NAME,
- their knowledge of the indication for TRADE NAME,
- their knowledge about the directions for use of TRADE NAME, and
- their receipt of, and perceived utility of, the Medication Guide and other counseling tools for TRADE NAME.

The pharmacist and patient surveys will be repeated every six months for the first two years of the program and trends will be analyzed. Modifications to the RiskMAP will be made as needed.

Claims Data

Cephalon will also purchase claims data as a surveillance tool to monitor prescribing patterns and, if possible, to assess the degree to which TRADE NAME is prescribed only to opioid-tolerant patients. The feasibility of using claims data further to provide meaningful information on clinical outcomes associated with the use of TRADE NAME

will be assessed before the database is utilized for such purposes. Whereas valuable insights into the RiskMAP and clinical outcomes might be obtained with a suitable database (eg, emergency room visits due to respiratory depression, emergency room visits because of accidental pediatric exposure; hospitalizations for opioid abuse; deaths associated with use of the medication, etc.), limitations of claims databases may not allow valid or reliable assessments to be made. For example, claims databases may be too limited in size to assess uncommon or rare adverse events, particularly if TRADE NAME use is not common, if patient turnover with the database is high, if events are not accurately coded, etc. However, should feasibility studies indicate that further evaluation of claims databases would be useful, then use of the claims data for these purposes will be pursued with an objective of gaining additional insights into the performance of the RiskMAP.

Other Surveillance Activities

As a follow-up to surveillance and monitoring activities, interventions may be warranted for any one or a combination of the risks described throughout this risk management plan. For example, if significant abuse or diversion is identified as occurring in a geographic area, Cephalon may employ education initiatives, as well as the use of local media and other communication vehicles, such as community outreach programs, to inform the community about the dangers and laws surrounding prescription opioid abuse.

Healthcare practitioners will be educated proactively and reactively on identifying patients who may be "doctor shopping" and/or have the potential for misuse and abuse of TRADE NAME. For example, a response after identification of a 'geographic hot spot' may be to follow-up with the prescriber(s) within that vicinity with a letter reminding them of TRADE NAME's CII scheduling status, risks associated with the drug, and the implications associated with its diversion. Other interventions may include community outreach as a technique to help educate a community that may be at particular risk. Cephalon will cooperate with and assist law enforcement agencies at a federal, state, and local level in cases of abuse or diversion of TRADE NAME.

Target Values

It is not possible to determine with any degree of confidence an acceptable level of noncompliance for these goals. Rather than set an 'a priori' standard for acceptable compliance, Cephalon proposes to establish a quality assurance procedure.

After reviewing the data obtained from spontaneous adverse event reports, surveys, and claims-based systems, an evaluation of performance will be made. Upon analysis of each departure from the RiskMAP, the potential causes of such departures will be assessed, and, if needed, changes to the RiskMAP will be made to improve performance. Analytical tools will be used, as feasible, to facilitate the process, (eg, decision trees, criticality indices). The intent of the assessment is to identify which tools have been most effective and which ones warrant modification to increase success in achieving the objectives of the RiskMAP.

Periodic evaluations will occur to monitor progress of the RiskMAP at meeting its objectives. Areas for improvement will be identified and the RiskMAP may be modified

based on these evaluations. Specific measures (included in the evaluations) will be monitored for progress against measured performance. If sufficient progress is not made, RiskMAP modifications will be made.

Time Frames and Progress Report Submission

RiskMAP evaluations will be conducted quarterly for the first two years of marketing, with a report of the evaluations submitted to the FDA. Subsequent to this time period, assessments of the RiskMAP will be made on an annual basis and Cephalon will provide the FDA with a report of its progress and any changes they have made to the program.

Table 5: Surveillance and Monitoring Activities

Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Spontaneous Adverse Event Reporting System	Expedited reporting of serious adverse events (SAEs) associated with abuse, misuse, or diversion.of TRADE NAME as well as SAEs associated with accidental exposure to TRADE NAME (including TESS data) or use by opioid non-tolerant individuals. Conduct periodic reviews of reports to discern any pattern(s) in departures from safe-product-use pathways of TRADE NAME.
1,2,3	Refine understanding of key points of intervention in FMEA analyses	FDA Cephalon	Pharmacovigilance	Literature Review	Regular structured review of scientific literature on (1) misuse, abuse, and diversion of TRADE NAME, (2) accidental exposures to TRADE NAME, and (3) SAEs associated with use of TRADE NAME by opioid non-tolerant individuals to discern any pattern(s) in departures from safe-product-use pathways of TRADE NAME.
2	Refine understanding of patterns of abuse or diversion of TRADE NAME	FDA Cephalon	Pharmacovigilance	Review National Surveys	National surveys on abuse and diversion, such as Drug Abuse Warning Network (DAWN), Monitoring the Future (MTF), National Survey on Drug Use and Health (NSDUH, formerly called NHDSA), will be reviewed to look for any signal or patterns of abuse or diversion associated with TRADE NAME.

(continued)

Table 5: Surveillance and Monitoring Activities (Continued)

Goal	Purpose	Primary Audience(s)	Tool Category	Tool	Description
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Prescriber surveys	Prescribers will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their patterns of TRADE NAME prescribing (eg, opioid vs. non-opioid tolerant), and (4) their assessment of the risk minimization tools (eg, use of, and reaction to, various Cephalon communications).
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Pharmacist surveys	Pharmacists will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their awareness and use of the carton checklist, Medication Guide, and other information about the product made available by Cephalon field representatives, and (4) their assessment of the value of counseling messages provided by major publishers of pharmacy counseling software.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Assessment of comprehension, knowledge, attitudes, and/or desired safety behaviors about drug safety risks	Patient surveys	Patients will be surveyed to assess (1) their knowledge of the key risks associated with the use of TRADE NAME, (2) their knowledge of the indication for TRADE NAME, (3) their knowledge about the directions for use of TRADE NAME, and (4) their receipt of, and perceived utility of, the Medication Guide and other counseling tools for TRADE NAME.
1,2,3	RiskMAP Evaluation	FDA Cephalon	Process measures that reflect desirable safety behavior & Outcome measures	Claims data	Cephalon will evaluate, via feasibility studies, whether the purchase of claims data as a surveillance tool will provide meaningful information on clinical outcomes associated with the use of ACCLEANYL.
1,2,3	Internal Auditing	Cephalon	Validation of internal process	TRADE NAME speaker bureau training	TRADE NAME speakers will verify that they have been trained on and understand the 3 principal risks identified in the RiskMAP.
1,2,3	External Auditing	Cephalon	Validation of external process	Validation of speaker bureau communication of risks	Cephalon field personnel will verify that TRADE NAME speakers present the information that focuses on the risks identified in the RiskMAP at each TRADE NAME promotional education program.

GLOSSARY OF TERMS

Abuse: Drug abuse (limited to medicinal products only) is defined as "a persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects (Volume IX of Pharmacovigilance; The Rules of Governing Medicinal Products in the EU).

Accidental Pediatric Exposure: All accidental pediatric (children <17 years of age) exposures including misguided uses or use facilitated by a non-healthcare professional, excluding intentional recreational use by an adolescent.

Diversion: The willful transfer of a drug from legitimate supply (manufacture, distribution, or storage in hospitals, pharmacies, physicians' offices) and/or patients for whom the drug has been prescribed to unauthorized users and/or for illegal sale.

F1 packaging: Packaging that meets the effectiveness specifications using the 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 effervescent fentanyl tablets, 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 one or more placebo test tablets, the package will fail for that particular child.

Failure Mode Effects Analysis (FMEA): A prospective procedure in which each potential failure mode in every subitem of an item is analyzed to determine its effect on other subitems and on the required function of the item.

Launch: The 6-month time period immediately following commercialization of a product, where commercialization means shipping a product to a wholesaler for subsequent distribution and sale.

Misuse: Use of a medication, prescribed by a physician, in a manner which is not prescribed.

Root-Cause Analysis: A process for identifying the basic or causal factor(s) that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event.

Safe product use pathway: A set of explicit instructions and control measures that describe the safe use of the product at appropriate intervention points including at the supply chain, at the point of prescribing, at the point of dispensing, during consumer storage and at the disposal of product.

Supply chain: Begins with Cephalon's receipt of fentanyl citrate through the manufacturing and packaging of TRADE NAME.

REFERENCES

American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. Glenview, IL: American Pain Society; 2003.

Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. Pain 1999;81(1-2):129-34.

Savage S. Long-term opioid therapy: assessment of consequences and risks. J Pain Symptom Manage 1996;11(5):274-86.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). *Guidance for Industry: Development and Use of Risk Minimization Action Plans*; March 2005.

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
1	Blister	Launch and ongoing: Tablets will be supplied in double-foil blister which meet F1 requirements and which have passed tests for child resistance and senior friendliness. This tool is designed to minimize the risk of accidental exposure to TRADE NAME.	Patients	3	L,O	√
2	Blister label	Launch and ongoing: The blister label contains warning information that TRADE NAME should be kept of the reach of children and that is only for patients already taking opioids; it also contains instructions for use.	Patients	1,3	L,O	√
3	Carton label	Launch and ongoing: The labeling of the carton will contain warning information, be color coded by strength, and will contain a reminder checklist to prompt the pharmacist to counsel the patient about the 3 principal risks associated with use of TRADE NAME. The carton label also directs the patient and/or caregiver to read the Medication Guide for important warnings.	Patients Pharmacists	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
4	Medication guide	Launch and ongoing: The TRADE NAME Medication Guide will emphasize the 3 principal risks associated with the use of TRADE NAME. Specifically it warns the patient of the potentially serious consequences, including death, that may occur when using TRADE NAME in opioid non-tolerant patients; it warns that the patient may become physically dependent on opioids and could become addicted to TRADE NAME; and lastly it warns that TRADE NAME is to be kept out of the reach of children and that TRADE NAME contains medicine that could be harmful or fatal to someone who has not been prescribed the medicine. It will go directly to patients via packaging the carton and will be made available to all prescribers and TRADE NAME-stocking pharmacies (via 800#, product-specific website and Cephalon sales representatives) for education and dissemination to patients.	Patients Pharmacists Prescribers	1,2,3	L,O	√
5	Package insert	Launch and ongoing: The package insert will contain a Boxed Warning about the life-threatening risks associated with the use of TRADE NAME in opioid non-tolerant patients; misuse, abuse and diversion; and accidental exposure to the medication.	Pharmacists Prescribers	1,2,3	L,O	√
6	Direct Risk communication by Cephalon field representatives	Launch and ongoing: Prescribers will be informed in person of the key messages and elements of the TRADE NAME RiskMAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for TRADE NAME abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.	Prescribers	1,2,3	L,O	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
7	Direct Risk communication by Cephalon field representatives	Launch: Pharmacists likely to dispense TRADE NAME will be informed in person of the key messages and elements of the TRADE NAME Risk MAP, including the potentially life-threatening risk of use by an opioid non-tolerant individual, the high potential for TRADE NAME abuse as well as the risk of misuse and diversion, and the potentially life-threatening risk of accidental use of TRADE NAME in children or adults.	Pharmacists	1,2,3	L	√
8	Educational Introductory Letter to Healthcare Professionals	Launch: Cephalon will develop and disseminate an educational TRADE NAME introductory letter reinforcing the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. At the time of launch, the letter will be disseminated via direct mail to 10,000 identified healthcare practitioner targets, 3,000 retail pharmacists likely to stock TRADE NAME, and the top 25 Pain Centers of Excellence.	Prescribers Pharmacists	1,2,3	L	√
9	Educational monograph for physicians	Launch: Cephalon will develop and disseminate a TRADE NAME educational monograph which will reinforce the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. The monograph will be disseminated at launch via direct mail to 10,000 identified healthcare practitioners and the top 25 Pain Centers of Excellence.	Prescribers	1,2,3	L	√

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
10	PharmAlert	Launch: Educational material that reinforces the 3 principal messages of the RiskMAP. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME. These will be distributed to 40,000 retail pharmacists.	Pharmacists	1,2,3	L	√
11	Physician education directed to Pain Centers of Excellence	Launch: Cephalon will contact each of the identified top 25 Pain Centers of Excellence to offer further educational opportunities to learn about TRADE NAME, including the 3 principal risks identified in the RiskMAP. Specifically risk of use by opioid non-tolerant individuals, the risks for misuse, abuse and diversion, and the risk of accidental exposure to TRADE NAME will be addressed. The educational platform for these offerings will include symposia and/or teleconferences.	Prescribers	1,2,3	L	√
12	Pharmaceutical compendia	Launch and ongoing: Cephalon will provide TRADE NAME information, including the 3 principal risks identified in the RiskMAP, to several well-known compendia such as Physicians' Desk Reference (PDR), American Hospital Formulary Service (AHFS), and Drug Facts and Comparisons.	Prescribers Pharmacists	1,2,3	L,O	

(continued)

APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
13	Counseling messages	Launch and ongoing: Cephalon will provide risk information to First Data Bank and/or other major publishers of pharmacy counseling software to educate the majority of retail pharmacists on the 3 principal risks associated with use of TRADE NAME. Specifically these messages will address that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Prescribers Pharmacists	1,2,3	L,O	√
14	Counseling aid	Launch and ongoing: In addition to the Medication Guide, Cephalon will develop a counseling aid to be used by healthcare professionals when advising and educating patients about TRADE NAME. This aid will include information about the 3 principal risks associated with use of TRADE NAME. Specifically the aid will include information addressing that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Patients Pharmacists Prescribers	1,2,3	L,O	√
15	Counseling aid	Launch and ongoing: Educational materials will be disseminated to pharmacists who attend wholesaler trade shows and pharmacy meetings. These materials will provide education on the 3 principal risks identified in the RiskMAP. Specifically these materials will include information addressing that TRADE NAME is to be used only by opioid-tolerant individuals; a risk of misuse, abuse and diversion is associated with TRADE NAME; and there is a risk of accidental exposure associated with the use of TRADE NAME.	Pharmacists	1,2,3	L,O	√

(continued)APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
16	Speaker training	Launch and ongoing: Cephalon will formally train speakers on aspects of TRADE NAME consistent with the risk information in the package insert, including the key elements and messages of the RiskMAP. Cephalon will also provide speakers with information which they must present, that focus on the risks identified in the RiskMAP. Prior to speaking on behalf of Cephalon, these speakers will verify that they understand the 3 principal risks associated with the use of TRADE NAME. Evaluations provided will monitor whether speakers presented the required risk information.	Prescribers	1,2,3	L,O	√
17	Training for Cephalon field representatives	Launch and ongoing: Cephalon field representatives will receive product-specific training covering the approved prescribing information for TRADE NAME, including the TRADE NAME RiskMAP. 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 information on the 3 principal risks identified in the RiskMAP.	Cephalon field representatives	1,2,3	L,O	√
18	Independent continuing medical education (CME)	Launch: Cephalon will support independent education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe TRADE NAME.	Prescribers Pharmacists	2	L	
19	Introductory Letter to Drug Diversion Authorities	Launch: Proactive communications to drug diversion control authorities to educate interested parties and alter them to safeguard against the potential diversion of TRADE NAME.	Drug diversion professionals	2	L	
20	Product returns and disposal	Launch and ongoing: Cephalon will accept returns for disposal of unwanted TRADE NAME. This will be a tool to minimize the amount of excess product available.	Patients	2,3	L,O	√

(continued)

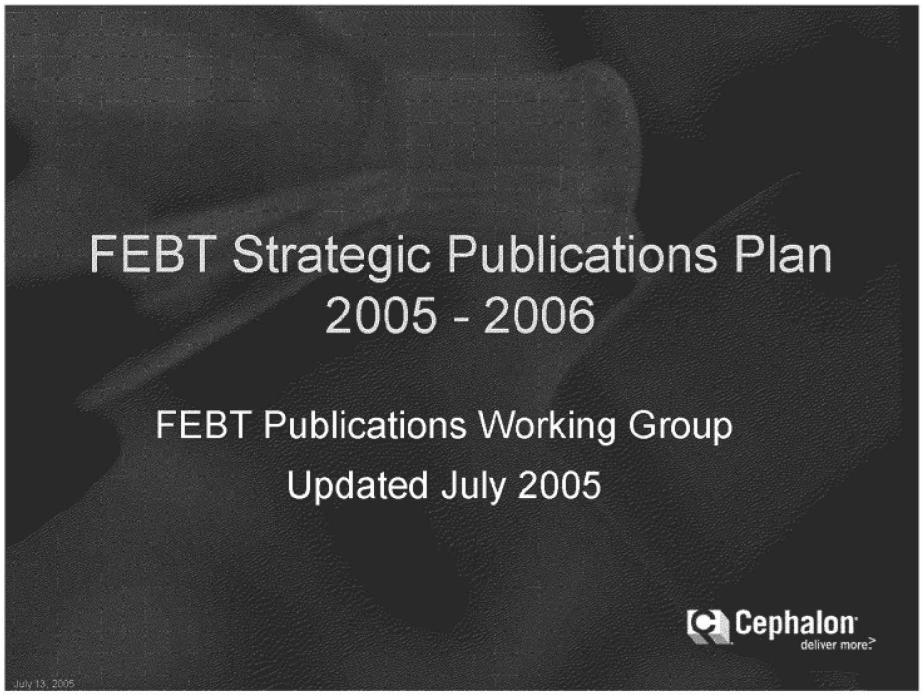
APPENDIX A TOOLS EMPLOYED IN THE TRADE NAME RISKMAP (CONTINUED)

No.	Tool	Description	Primary Audience	Goal(s)	Timing 0=ongoing L=launch	Metrics
21	Physician and Pharmacist education	Ongoing (response to surveillance): 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 the specific need (eg, symposium, teleconferences, print materials, etc.)	Prescribers Pharmacists	2	O	√
22	Toll-free number	Launch and ongoing: Poison control number for accidental ingestions.	Patients	3	L,O	
23	Reports of diversion and abuse	Launch and ongoing: Cephalon will attempt to implement an active monitoring system (eg, RADARS) at the time of the launch of TRADE NAME. Reports from the National Association of Drug Diversion Investigators (NADDI) will be actively monitored and screened for information on TRADE NAME.	Drug Diversion Professionals	2	L,O	
24	Physician education (targeted to members of professional societies)	Launch: Professional societies will be contacted to offer educational opportunities to learn about TRADE NAME and key messages and risks described in the RiskMAP, including the 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.	Prescribers	2	L	√

APPENDIX B
CHILD RESISTANT PACKAGING PROTOCOL REPORT

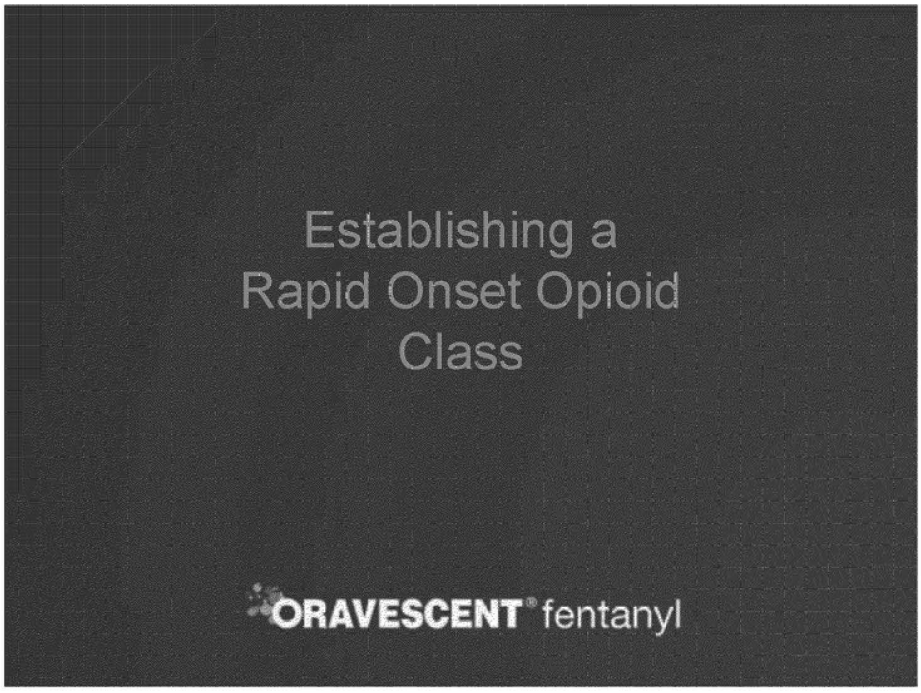
Appendix 5 – FEBT Publication/Communication Plan

NOTE: Please refer to ISCP Web site for full presentation.



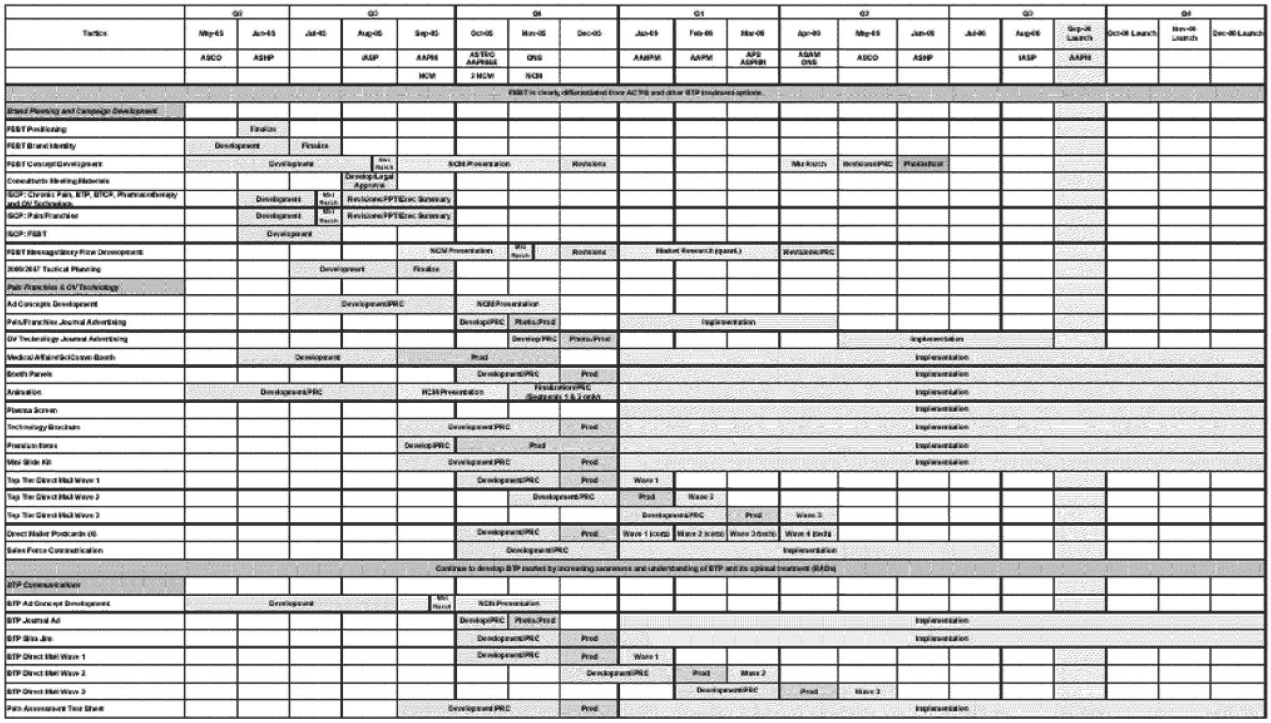
Appendix 6 – Rapid-Onset Opioid Situation

NOTE: Please refer to ISCP Web site for full presentation.



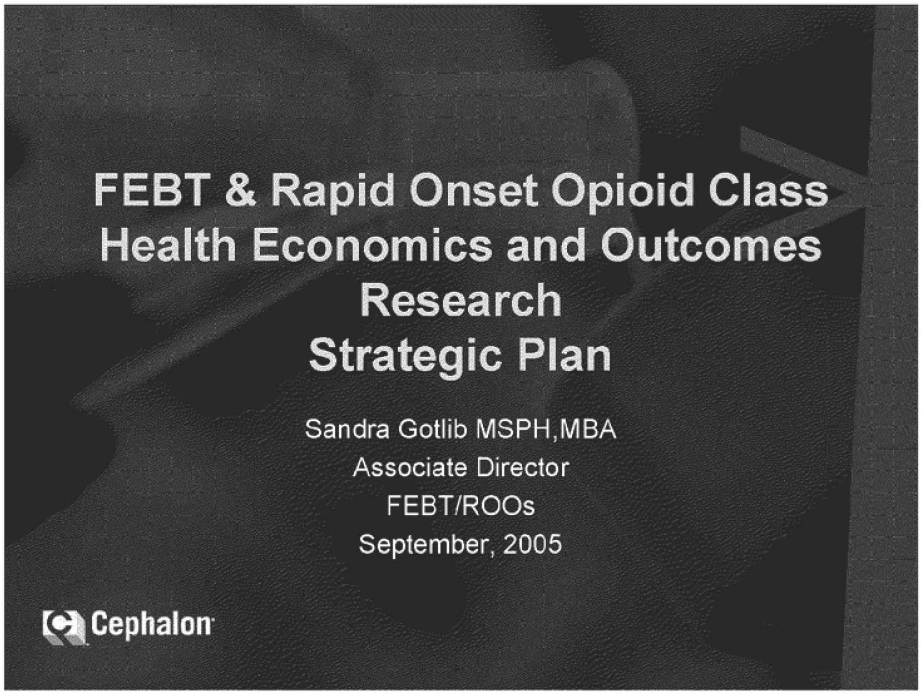
Appendix 7 – Palio Tactical Time Line

NOTE: Please refer to ISCP website for electronic version



Appendix 8 – Health Economic Outcomes Research Plan

NOTE: Please refer to ISCP Web site for full presentation.



Appendix 9 – Integrated Strategic Communication Plan

OraVescent Technology			
OraVescent Technology Overview	OraVescent is a breakthrough drug delivery technology utilizing effervescence in a tablet for rapid, efficient transport of active drug across the buccal mucosa	• Effervescent buccal tablets deliver drug faster and more efficiently than traditional oral delivery and conventional oral transmucosal delivery systems (eg, lozenge and sublingual delivery) (Pather 2001) • Efficient transport of active drug across the buccal mucosa minimizes first-pass metabolism (Fukodo 2005)	• OraVescent technology has potential applications in highly lipophilic compounds • OraVescent technology has potential applications in compounds that are weakly basic
Effervescence	OraVescent technology optimizes drug delivery through an effervescence reaction (Pather 2001)	• OraVescent buccal tablets employ effervescence to bring about a dynamic pH shift that enhances dissolution and optimizes the speed and extent of drug absorption. (Pather 2001)	• Patient places OraVescent tablet in the buccal cavity, where saliva causes an immediate effervescence reaction (Pather 2001) • During effervescence, the nontoxic citric acid and sodium bicarbonate in OraVescent form carbonic acid (Pather 2001) • Carbonic acid drives down the pH, enhancing dissolution of the ionized form of the drug (Pather 2001) • Carbonic acid dissociates into carbon dioxide and water. The carbon dioxide bubbles out of the saliva or passes across the

			mucosa (Pather 2001) • The loss of carbon dioxide represents a loss of acid in the system, which now contains an excess of bicarbonate. This raises the pH and causes the ionized form of the drug to become un-ionized, favoring absorption (Pather 2001) • Carbon dioxide has been hypothesized to have an effect on epithelial permeability. Preclinical research suggests that carbon dioxide may promote drug absorption by altering the paracellular pathway (Eichmann 1998)
Ease of Use	OraVescent buccal tablets offer discreet, convenient self-administration for patients	• Simplified self-administration without water • Discreet dosage form may improve patient compliance	• OraVescent buccal tablets dissolve passively in the mouth without the need for active administration

Chronic Pain			
Definition of Chronic Pain	Chronic pain is pain that lasts beyond the expected time for healing of an injury or insult (>3 months) (National Pharmaceutical Council 2005)		
Components of Chronic Pain	Chronic pain typically has 2 components: persistent pain and breakthrough pain (BTP) (American Cancer Society 2005)	• Persistent pain is baseline pain that is continuous throughout the day • BTP is a transitory exacerbation, or flare, of moderate-to-severe pain that occurs in patients with otherwise stable persistent pain (Portenoy 1990, Mercadante 2002)	
Prevalence of Chronic Pain	About 50 million of the estimated 75 million Americans who live with "serious pain" suffer from chronic pain (American Pain Foundation 2005)		
Categories and Characteristics of Chronic Pain	Chronic pain has traditionally been categorized as a symptom of other diseases (eg, cancer), but current thinking recognizes it as a distinct disease state	• Chronic pain may be caused by injury (eg, trauma, surgery), malignant conditions, or a variety of chronic non-life-threatening conditions (eg, arthritis, fibromyalgia, neuropathy) (National Pharmaceutical Council 2005) • Chronic pain may be continuous or intermittent with or without acute exacerbations (National Pharmaceutical	• Chronic pain may be nociceptive, neuropathic, or mixed (National Pharmaceutical Council 2005) • Nociceptive pain arises from the stimulation of pain receptors (nociceptors) when body tissues are damaged (Douglass 2005) • Neuropathic pain occurs when nerve pathways are damaged or function

		Council 2005) • The biochemical mechanisms of the sensation of pain are the same in cancer and noncancer chronic pain conditions (Turk 2002)	abnormally. It can occur independently of nociceptive pain or in conjunction with it (Douglass 2005)
Diagnosis and Treatment of Chronic Pain	Chronic pain is complex and may be comprised of 2 components, persistent pain and BTP (American Cancer Society 2005). Each component requires independent assessment and targeted treatment (Bennett 2005b)	• Diagnosing and managing chronic pain requires a substantial time commitment • The medical community has not reached consensus on optimal diagnosis and treatment guidelines • Persistent pain is typically managed with around-the-clock (ATC) medications (Bennett 2005b) • Some physicians avoid prescribing scheduled medications (eg, opioids) due to fears of abuse, diversion, or regulatory scrutiny (Savage 1996)	
Economic Impact of Chronic Pain	Chronic pain has a significant economic impact on patients and society	• Annual US cost of pain-related lost productivity, including absence, is approximately $61.2 billion (Stewart 2003) • Almost 50% of Americans seek medical care each year for pain, making pain the single most frequent reason for a physician consult in the United States (Bennett 2005a)	• In one study, 76% of patients with cancer experienced at least one pain-related expense (average: $891/month) (Fortner 2003)
Physical and Psychosocial Impact of Chronic Pain	Chronic pain disrupts sleep and normal living, ceases to serve a protective function, and, instead, degrades health and functional capability	• Pain is associated with feelings of frustration, bitterness, and anxiety, which are common for both the patient and his or her family (McNeely 2000) • Chronic pain is	• Chronic pain has a negative effect on physical and psychosocial well-being, including mood, sleep, and ability to work or enjoy activities

	(National Pharmaceutical Council 2005)	associated with irritability, social withdrawal, depressed mood and vegetative symptoms (eg, changes in sleep, appetite, libido), disruption of work, and social relationships capability (National Pharmaceutical Council 2005)	(Caldwell 1999)
Breakthrough Pain			
Definition of BTP	BTP is a transitory exacerbation, or flare, of moderate-to-severe pain that occurs in patients with otherwise stable persistent pain (Portenoy 1990, Mercadante 2002)		
Characteristics of BTP	• Onset of BTP is rapid, with escalation to maximum intensity in as little as 3 minutes (Portenoy 1990, Portenoy 1999) • BTP is often of moderate-to-severe intensity (Zeppetella 2000) • Approximately 40% to 50% of BTP episodes are unpredictable (Bennett 2005a) • The average duration of a BTP episode is 30 to 60 minutes (Portenoy 1990, Fine 1998, Portenoy 2005, Simon 2005, Bennett 2005c) • The average	• Episodes of BTP are often unpredictable. For episodes that are predictable, it is nearly impossible to predict duration or time to peak severity (Hwang 2003, Bennett 2005a)	

	number of BTP episodes is 2 to 4 per day (Portenoy 1990)		
Categories of BTP	Evidence has shown that BTP occurs in patients with both cancer and noncancer chronic pain	• BTP in patients with cancer is well recognized and well defined • BTP in patients with noncancer chronic pain, though less well studied, has been shown to have similar characteristics to BTP in patients with cancer	• BTP can be categorized as idiopathic, incident/predictable, incident/unpredictable, or end-of-dose failure
Prevalence of BTP	Up to 64% of patients with chronic cancer pain and 74% of patients with chronic noncancer pain experience breakthrough pain (Portenoy 1990, Portenoy 2005)		
Recognition of BTP	BTP is underrecognized due to a lack of validated assessment tools, adequate treatment guidelines, and education	• Physicians have no validated chronic pain assessment tool that includes a specific evaluation for BTP • Current pain treatment guidelines have only limited recognition of BTP • Historically, the pain community has not stressed the importance of physician education on BTP	
Treatment of BTP	BTP requires independent assessment and targeted treatment	• Opioids are the primary pharmacological treatment for BTP (Bennett 2005b) • Despite the current BTP treatment paradigm (10%-20% of around-the-clock [ATC] opioid), data have shown no correlation between the dose of the ATC opioid medication and the	

		dose required to treat BTP (Christie 1998) • Increasing the dose of ATC pain medications to treat BTP often results in overmedication and increased side effects such as sedation, constipation, and confusion • While oral short-acting opioids (SAOs) are commonly used to treat BTP, their relatively slow onset of action makes them a poor fit for the rapid onset of BTP (Bennett 2005b) • The preferred BTP treatment would provide rapid analgesia and a duration of effect that matched a typical BTP episode. This profile could be offered by a lipophilic rapid onset opioid (ROO)	
Economic Impact of BTP	BTP has a significant economic impact on patients and society	• Among patients with cancer, total annual cost of pain-related hospitalizations and physician office visits was 5 times greater for patients with BTP than for patients without BTP ($12,000 vs $2,400) (Fortner 2002) • Among patients with cancer, those with BTP are 2.5 times more likely to seek care in an emergency department than those without BTP (Fortner 2002) • Among patients with cancer, those with BTP experience 2.5 times more hospitalizations per year than those without BTP (1.0 vs 0.4) (Fortner 2002)	• Among patients with cancer, those with BTP have higher direct pain-related costs than those without BTP ($1,080/year vs $750/year) (Fortner 2003)
Physical and Psychosocial Burden	BTP has been associated with	• BTP has been shown to predict poor medical outcomes in patients	

of BTP	functional impairment and psychological distress (Portenoy 1999, Goudas 2005)	with cancer, and is associated with significant patient morbidity, decreased functioning, and increased levels of anxiety and depression (Bennett 2005a, Caraceni 2004, Portenoy 1999)	
Rapid Onset Opioid (ROO)			
Definition of ROO	A rapid onset opioid (ROO) is an opioid with an onset of analgesia of 15 minutes or less	• Short-acting opioids (SAOs) have an onset of analgesia of 30 to 40 min (Bennett 2005b)	
Classification of ROO	ROOs are an emerging subclassification of pain medications based on onset, rather than duration of analgesia *Note: "Key drug type" to be used in communication to managed care*	• The current opioid classification is based on duration of analgesia, either long acting or short acting, with no differentiation based on onset of analgesia • Due to the number of rapid onset products in development and their unique benefit profile, further subclassification of opioids based on onset of analgesia is emerging	• ROOs may have a different risk profile than SAOs, suggesting the need for further research • Appropriate patient selection and education may be required when prescribing ROOs
Efficacy	The ROO efficacy profile (rapid onset, moderate duration) closely matches the characteristics of a typical BTP episode, thereby providing a more appropriate treatment option than conventional SAOs		

Pain Franchise			
Breakthrough Technology	Cephalon is applying breakthrough technologies to the challenges of pain management	• Applied oral transmucosal lozenge for delivery of fentanyl (OTFC) • Applied OraVescent technology for rapid delivery of fentanyl (FEBT)	
Innovative Treatments	Cephalon is delivering innovative treatments for pain	• Commercialized OTFC (ACTIQ) in the US market • Preparing to introduce fentanyl effervescent buccal tablet (FEBT) in the US market	
Pain Education	Cephalon is advancing the understanding of pain	• Introduced industry-leading risk management program for OTFC (ACTIQ) • Sponsor of numerous educational activities and forums on pain management to assist in educating patients and physicians	

For internal use only to standardize communications. Suggested but not required.

References:

American Cancer Society. Breakthrough Cancer Pain: Questions and Answers. Available at: http://www.cancer.org/docroot/MIT/content/MIT_7_2x_Breakthrough_Cancer_Pain_Questions_and_Answers.asp?sitearea=MIT&viewmode=print&. Accessed November 7, 2005.

American Pain Foundation. Fast Facts About Pain. Available at: http://www.painfoundation.org/print.asp?file=Library/FastFacts.htm. Accessed November 7, 2005.

Bennett D, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain–part I assessment. *Pharm Ther.* 2005(a);30:296-301.

Bennett D, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain–part II management. *Pharm Ther.* 2005(b);30:354-361.

Bennett DS, et al. Presented at: American Academy of Pain Medicine. Palm Springs, Calif. February 24, 2005(c).

Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J *Rheumatol*. 1999;26:862-9.

Caraceni A, Martini C, Zecca E, et al: for the Working Group of an IASP Task Force on Cancer Pain. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med*. 2004;18:177-83.

Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol*. 1998;16:3238-45.

Douglass AB. Pain. In: Rakel RE, Bope ET, eds. *Conn's Current Therapy 2005*. 57th ed. Philadelphia, Pa: WB Saunders; 2005:1-5.

Eichman JD, Robinson JR. Mechanistic studies on effervescent-induced permeability enhancement. *Pharm Res*. 1998;15:925-930.

Fine PG, Busch MA. Characterization of breakthrough pain by hospice patients and their caregivers. *J Pain Symptom Manage*. 1998;16:179-183.

Fortner BV, Demarco G, Irving G, Ashley J, Keppler G, Chavez J, Munk J. Description and predictors of direct and indirect costs of pain reported by cancer patients. *J Pain Symptom Manage*. 2003;25:9-18.

Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain*. 2002;3:38-44.

Fukudo K. Intravenous opioid anesthetics. In: Miller RD. *Miller's Anesthesia*. 6th ed. San Francisco, Calif: Churchill Livingstone; 2005:416.

Goudas LC, Bloch R, Gialeli-Goudas M, Lau J, Carr DB. The epidemiology of cancer pain. *Cancer Invest*. 2005;23:182-90.

Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain*. 2003;101:55-64.

McNeely C. The role of the family in the treatment of chronic pain. *The Pain Practitioner/American Academy of Pain Management*. 2000;1:5-6.

Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer*. 2002;94:832-839.

National Pharmaceutical Council. Pain: current understanding of assessment, management, and treatments. Available at: http://www.jcaho.org/news+room/health+care+issues/pain_mono_npc.pdf. Accessed October 27, 2005.

Pather SI, Siebert JM, Hontz J, Khankari RK, Gupte SV, Kumbale R. Enhanced buccal delivery of fentanyl using the OraVescent drug delivery system. *Drug Deliv Tech.* 2001;1-8.

Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain.* 1990;41:273-281.

Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain.* 1999;81:129-134.

Portenoy RK, et al. Poster presented at: Annual Meeting of the American Pain Society; March 30-April 2, 2005; Boston, Mass. Poster 698.

Savage SR. Long-term opioid therapy: assessment of consequences and risks. *J Pain Symptom Manage*. 1996;11:274-86.

Simon S, et al. Presented at: American Academy of Pain Medicine; February 24, 2005; Palm Springs, Calif.

Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290:2443-2454.

Turk DC. Remember the distinction between malignant and benign pain? Well, forget it. *Clin J Pain*. 2002;18:75-76.

Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage.* 2000;20:87-92.

Appendix 10 – Market Research Plan

FEBT Market Research Plan

Prelaunch

Study Name	Time
ISCP medical terminology + OV message	Q3 '05
Pain franchise image + message study	Q3 '05
FEBT branding elements	Q3 '05
BTP awareness testing (ad boards)	Q3 '05
Psychographic BTP patient study	Q3 '05
Promotional response	Q4 '05
FEBT message testing	Q4 '05
Pricing analysis	Q4 '05
FEBT final concept testing	Q1 '06
Baseline ATU	Q2 '06

Postlaunch (tentative research plan)

Study Name	Time Postlaunch
Weekly data trend analysis	Ongoing from launch
Managed care data tracking	Ongoing from launch
Diary study (current treatment patterns)	Ongoing from launch
Sales force effectiveness (5 monthly waves) - Message recall - Competitive response - Believability - Awareness - Penetration	2 months
ACTIQ loyalist switching study	3 months
Campaign tracking	6 months
Patient chart audit	3 quarters

Appendix 11 – Miscellaneous Tables and Charts

Table 1

Product Conversion Analogs Analysis

The products included in the conversion analysis are listed in the table below:

				Switch Rates[1]	
Product	**Precursor**	**Product Indication(s)**	**Time to Switch**	**5 months**	**10 months**
Adderall XR	Adderall	• ADHD	• 4 months	54%	74%
Clarinex	Claritin	• Allergies	• 12 months	42%	43%
Detrol LA	Detrol	• Incontinence	• Detrol patent expires 2012	38%	67%
Lexapro	Celexa	• Depression, anxiety	• 18 months	30%	63%
Nexium	Prilosec	• GERD, erosive esophagitis	• 20 months	14%	31%
Paxil CR	Paxil	• Depression, anxiety	• 18 months	11%	25%
Prozac Weekly	Prozac	• Depression	• 5 months	5%	5.5%
Sarafem	Prozac	• Premenstrual dysphoric disorder	• 12 months	2%	5%
Mean				*24.5%*	*39.2%*

[1] This is the TRx of the successor product as a percentage of the average precursor prescriptions 6 months before the launch of the successor.

Note: Switch rates alone are not indicative of the quality of a company's marketing tactics. For example, Adderall XR was able to achieve a high switch rate given Adderall's fairly low annual sales ($250 million in 2000) and the high market demand for a once-daily for ADHD.

Nexium/Prilosec's rate is not the highest because of Prilosec's significant sales volume (>$4 billion in 2000) and relatively low immediate demand for a new proton pump inhibitor.

Table 2

Breakthrough Pain – First-Line Therapy

		Low/Non Users			
	Heavy/Med Users of ACTIQ	Non-ACTIQ Users	Pain Specialists	PCP	Other
Moderate BTP pain					
Hydrocodone	65%	67%	77%	72%	59%
Oxycodone + acetaminophen	52%	26%	44%	28%	23%
Oxycodone	46%	17%	37%	14%	20%
ACTIQ	30%	6%	17%	6%	5%
Short-acting morphine	29%	12%	19%	10%	13%
Propoxyphene napsylate	25%	21%	27%	19%	22%
Acetaminophen + codeine	24%	27%	22%	31%	22%
Hydromorphone	15%	10%	11%	10%	9%
Severe BTP pain					
Oxycodone	57%	28%	51%	27%	27%
ACTIQ	55%	9%	28%	8%	7%
Oxycodone + acetaminophen	48%	37%	56%	35%	37%
Hydrocodone	41%	48%	48%	49%	46%
Short-acting morphine	36%	26%	28%	29%	23%
Hydromorphone	32%	17%	24%	17%	18%
Acetaminophen + codeine	16%	16%	14%	19%	12%
Propoxyphene napsylate	13%	12%	17%	14%	9%

Blue = combination SAO Yellow = pure SAO White = respondent did not specify type of SAO

Source: Pain Market Dynamics Study, March 2005.