Contacts

Name &	Fred Naraghi M.D.	**Gender:**	
Address:	1580 Valencia Street Suite 703 San Francisco, CA 94110 US	**Phone:**	415-642-0707
		FAX:	
		EMail:	
		Misc:	
Class:	1A	**Greeting:**	
Type:	HCP	**Salutation:**	Dr.
Specialty:	(Blank)	**Degree:**	M.D.

Case Information

Language	English	**Rep Type**	PCS Territory Sales S	**Service Rep**	ML
Division	US	**Rep Contact**	55686	**Referred To**	ML
Department	Medical Information	**Case Type**	Medical Information	**Entered**	3/22/2007 8:00:37 A
Status	Completed	**Priority**		**Received**	3/22/2007 8:00:36 A
Request Via	Representative	**Source**	E-MIRF-Visit	**Completed**	3/22/2007 2:16:32 P
Rep/Terr#	32220001	**Handling**	Cephalon-Mail	**First Resp**	3/22/2007 0
Rep Name	Timothy Fortescue	**Entry Period**	Cephalon	**Time Spent**	0

Notes

Audit

Text Information	Numeric	Date	Yes/No
use in low back pain	0		No

	Product	Product Description	NDC Number	Category	Topic	Close Date
Product	FENT	FENTORA		LBPAIN		3/22/2007
Question	Can Fentora be used for low back pain?					
Response	FENT014					
Document						
Product	FENT	FENTORA		NCP		3/22/2007
Question	03/21/2007					
Response						
Document						

Response Letter

Letter	Date	Status	Contact Name	Format	Opening	Closing
794376		Completed	Fred Naraghi	Cover Letter	COVER Rep	UNIV Closin

Signature	Language	Envp	Label	Count	Merge Date	User
PSG	English	No	No	0	3/22/2007	ML

Print	Enc	Print Date	Print User	Edit Date	Edit User
Yes	No	3/22/2007	ML		

Fax	Enc	Fax Date	Fax User	Submit Date	Submit User
No	No			3/22/2007	ML

E-mail	Enc	E-mail Date	E-mail User	Rep Date	Rep User
No	No			3/27/2007	JEM

Product	Document ID	Document Title	Category	Topic
FENT	FENT014	FENT014- Use for the management of breakthro	EFF	BTP-NC

Enclosure Description	Quantity	Location
FENT014- Use for the management of b	-1	
FENTORA - Current Approved Prescribi	1	
Cephalon - Medical Information Survey	1	

Response Letter

Letter	Date	Status	Contact Name	Format	Opening	Closing
794377		Completed	Fred Naraghi	Standard Letter	Open E-MIR	Clos E-MIRF

Signature	Language	Envp	Label	Count	Merge Date	User
SL	English	No	No	0	3/22/2007	ML

Print	Enc	Print Date	Print User	Edit Date	Edit User
Yes	No	3/22/2007	ML		

Fax	Enc	Fax Date	Fax User	Submit Date	Submit User
No	No			3/22/2007	ML

E-mail	Enc	E-mail Date	E-mail User	Rep Date	Rep User
No	No			3/27/2007	JEM

Product	Document ID	Document Title	Category	Topic
FENT	E-MIRF Audit	E-MIRF Audit	NCP	

March 22, 2007

Fred Naraghi, M.D.
1580 Valencia Street
Suite 703
San Francisco, CA 94110

Dear Dr. Naraghi:

Your Cephalon Sales Specialist, Timothy Fortescue, has forwarded your request for information regarding FENTORA® (fentanyl buccal tablet). In response to your inquiry we have enclosed the following information:

• Use for the management of breakthrough pain in opioid-tolerant patients with chronic noncancer pain conditions.

FENTORA Product Summary

FENTORA, a potent opioid analgesic, was specifically designed, studied and approved for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.[1] Patients considered opioid tolerant are those who are taking at least 60 mg of morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

FENTORA is formulated as a flat-faced, round, beveled-edge, white tablet of fentanyl citrate, and is intended for buccal mucosal administration. After removing FENTORA tablet from the blister unit package, the entire tablet should **immediately** be placed and retained within the buccal cavity (between the upper cheek and gum above a rear molar) for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

FENTORA **must not** be used in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain. Patients and caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child, and thus, must keep all tablets out of the reach of children, and to properly discard of any unused tablets as soon as they are no longer needed.

In a pivotal trial of FENTORA, onset of efficacy was demonstrated within 15 minutes in some patients, with duration of efficacy demonstrated up to 60 minutes (last time point measured). For

patients with unrelieved pain, redosing may occur 30 minutes after start of administration of FENTORA using the same dosage strength.

Due to the higher bioavailability of fentanyl in FENTORA, when converting patients from other oral fentanyl products, including Actiq® (oral transmucosal fentanyl citrate) or OTFC, FENTORA should not be substituted on a mcg per mcg basis. FENTORA should be initiated at 100 mcg, and patients should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. For additional information, please see the dosing conversion chart and dosage and administration instructions in the enclosed FENTORA prescribing information.

During premarketing clinical trials, FENTORA was generally well tolerated at doses of 100 mcg to 800 mcg. The most commonly observed events seen with FENTORA are typical of opioid side effects. Opioid side effects should be expected and managed accordingly. The most common (≥10%) adverse events observed in clinical trials of FENTORA were nausea, vomiting, application site abnormalities, fatigue, anemia, dizziness, constipation, edema, asthenia, dehydration, and headache. Most of the reported adverse events were mild to moderate in severity. There has been no attempt to correct for concomitant use of around-the-clock opioids, duration of FENTORA therapy, or cancer-related symptoms.

Please see the enclosed FENTORA package insert, including boxed warning for full prescribing information.[1]

We hope this information is helpful. If you have additional questions, or would like to receive a copy of the references, please feel free to contact Cephalon Professional Services at (800) 896-5855 or send an e-mail to USMedInfo@Cephalon.com. Your Cephalon Sales Specialist may also be able to provide you with certain references.

Sincerely,
<Signature>

Professional Services and Medical Information
Medical Services Department

IRMS: 302000

Enclosures: FENTORA - Current Approved Prescribing Information.
Cephalon - Medical Information Survey

Use of *FENTORA*™ (fentanyl buccal tablet) [C-II] for the management of breakthrough pain in opioid-tolerant patients with chronic noncancer pain conditions

The cited material may include information that is not part of the FDA-approved product labeling. Please consult the enclosed FENTORA package insert including boxed warning for full prescribing information.[1]

Please note, *FENTORA* is **not** indicated for the management of breakthrough pain in patients with chronic noncancer pain conditions.

Background Information: Breakthrough Pain

In patients who have chronic pain, two components are often present: persistent pain (continuous pain lasting 12 or more hours/day) and breakthrough pain (BTP), which is a transitory flare of moderate-to-severe pain that occurs in patients with otherwise stable, controlled persistent pain.[2,3,4] These flares of pain or BTP can occur in patients with chronic pain regardless of the origin (cancer or noncancer conditions such as low back pain, arthritis or diabetic neuropathy).[5]

Depending on the patient population examined, approximately 51% to 89% of cancer patients with controlled persistent pain experience BTP.[3,4,6] Based on the results from one survey of 164 inpatients with cancer pain, the onset of BTP is often sudden, reaching maximal intensity within 3 minutes in 43% of patients, and has a median duration of 30 minutes (range: 1-240 minutes).[3] In this survey, cancer patients experienced an average of six BTP episodes per day.[3]

Based on the two surveys discussed below, the prevalence of BTP in patients with chronic noncancer pain is generally similar to that in patients with cancer pain. A recent survey of 228 outpatients with chronic noncancer pain and controlled persistent pain found that the prevalence of BTP was 74%.[7] Of the 717 patients screened, a total of 228 patients were eligible for the study. In this study, 74% (n=168) of the patients surveyed described one or more types of BTP episodes.[7] The most common chronic pain conditions among patients with BTP included low back pain, neuropathy, complex regional pain syndrome, cervical neck pain and arthritis. The median frequency of episodes per day was 2 (range: <1 per week to 12 per day). The median time to maximum intensity was 10 minutes (range: 0-180 min). Median duration of BTP episodes was 60 minutes (range: 1-720 min), and one third (33%) of the BTP episodes had a duration of 30 minutes or less. Onset could not be reliably predicted by patients in approximately 84% of the BTP episodes. The authors concluded that these findings demonstrated that BTP is highly prevalent and varied in patients with chronic noncancer pain, and shares similar characteristics to those reported in cancer patients.

One prospective survey of 43 patients with noncancer terminal disease in hospice care reported a prevalence of BTP in 63% of patients.[8] The average number of BTP episodes per day was 5 (range 1-13), of which 54% occurred suddenly. Many BTP episodes (56%) were unpredictable and 73% of all BTP episodes lasted 30 minutes or less. The authors concluded that these

findings suggested that BTP is common, frequent, short-lasting and often unpredictable in patients with noncancer terminal disease.

Breakthrough pain associated with cancer BTP is typically managed with immediate-release, short-acting oral opioids, taken as needed in addition to an around-the-clock (ATC) opioid regimen for the persistent pain. The use of this treatment strategy has been extrapolated to treat BTP in selected patients with chronic noncancer pain conditions.[5] Conventional short-acting opioids may not be optimal for many patients since the time to onset of analgesia (typically 30-60 minutes) is relatively delayed to the time course of most BTP episodes which can often be unpredictable, and can peak rapidly. Therefore, there is a need for analgesics with a more rapid onset of effect which provide faster pain relief, thereby improving the overall effectiveness of therapy.

FENTORA

OraVescent® Drug Delivery Technology

FENTORA employs the OraVescent drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that the transient salivary pH changes accompanying the reaction, in the microenvironment of the oral mucosa surrounding the tablet, may optimize tablet dissolution (at a lower pH) and membrane permeation (at a higher pH) across the buccal mucosa.[1,9,10]

This unique delivery system allows fentanyl to dissolve quickly, and allows for approximately 50% of the total dose to be rapidly and directly absorbed through the buccal mucosa into systemic circulation. Fifty percent of the dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract (GI) and first pass metabolism prior to becoming systemically available. Of the amount swallowed, approximately 17% becomes systemically available and this portion contributes to the prolonged duration of analgesia observed in clinical trials. The absolute bioavailability of FENTORA is 65%.

Clinical Experience

Use of FENTORA in chronic cancer pain patients

FENTORA is indicated for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking oral morphine ≥60 mg/day, transdermal fentanyl ≥25 mcg/hr, oxycodone ≥30 mg/day, oral hydromorphone ≥8 mg/day or an equianalgesic dose of another opioid for a week or longer.

In a randomized, placebo-controlled study of opioid-tolerant patients with cancer-related BTP, *FENTORA* was efficacious and well tolerated.[11,12]

Use of FENTORA in chronic noncancer pain patients

FENTORA is **not** indicated for the management of breakthrough pain in patients with chronic noncancer pain conditions.

Cephalon is conducting several clinical trials to evaluate the efficacy, safety, and tolerability of *FENTORA* in opioid-tolerant patients with BTP associated with chronic noncancer pain conditions.

Summarized below are the results of two completed randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of *FENTORA* for the treatment of BTP in chronic noncancer pain conditions in patients who are opioid-tolerant. One study was conducted in patients with BTP associated with chronic low back pain (Study 1) and the other in patients with BTP associated with chronic neuropathic pain (Study 2). In addition, the interim results of one ongoing 18-month, open-label safety study for the treatment of BTP in opioid tolerant patients with chronic noncancer pain are also summarized below for your review and consideration.

Double-blind, Placebo-controlled Studies

The study design of the two noncancer efficacy studies (Study 1 and Study 2) were similar to each other. The initial open-label dose titration phase identified an effective dose of *FENTORA* (100, 200, 400, 600, 800-mcg). An effective dose was defined as the dose strength where one tablet of *FENTORA* provided satisfactory relief of BTP within 30 minutes for $\geq$ 2/3 episodes without unacceptable adverse events (AEs). During the dose titration period, patients discontinued the study if they did not obtain satisfactory relief from BTP at any dose including the maximum dose of 800 mcg of *FENTORA* or if they experienced intolerable AEs. The patients who entered the double-blind phase were randomized to 1 of 3 sequences in which 9 BTP episodes were treated. Six episodes were treated with *FENTORA* and 3 were treated with placebo.

In both the studies (Study 1 and Study 2), pain intensity (PI) was measured at 5, 10, 15, 30, 45, 60, 90, and 120 minutes following treatment. Pain intensity differences (PID) between each time point and pre-treatment pain were calculated. The sum of pain intensity differences from 5 minutes though 60 minutes ($SPID_{60}$) after administration of study drug was the primary efficacy measure in both studies. Secondary outcome measures included PID and pain relief (PR) at each time point, the proportion of treated BTP episodes with a $\geq$33% and $\geq$50% reduction in PI score following treatment, patients' assessment of time to meaningful PR, and the proportion of BTP episodes that required the use of usual rescue BTP medication.

Study 1 – BTP Associated with Chronic Low Back Pain

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy and tolerability of *FENTORA* compared to placebo in alleviating BTP in adult opioid-tolerant patients with chronic low back pain. [13,14,15,16]

Patients had a diagnosis of chronic low back pain associated with degenerative disc disease (70%), osteoarthritis (5%), spondylolisthesis (5%), or other eligible low back pain etiologies (18%), resulting in functional disability of at least 3 months duration.
In addition, eligible patients experienced 1-4 BTP episodes per day with a duration of less than 4 hours for each BTP episode and were managed with stable doses of ATC opioid medications (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 mcg/hr, oxycodone ≥30 mg/day, oral hydromorphone ≥8 mg/day or an equianalgesic dose of another opioid, for 7 days or longer prior to enrollment into the study) for their persistent pain.

Key results from this placebo-controlled study 1 showed the following:

Patient Disposition

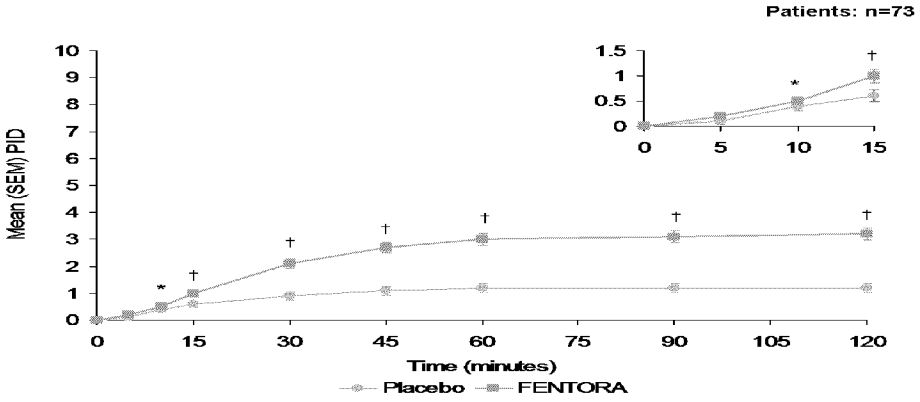
- The mean age of the patients in this study was 48 years, the majority were female (54%), and 89% were Caucasian.
- During dose titration, 74% (77/104) of patients completed this period and 26% (27/104) of patients discontinued participation (11 due to intolerable adverse events, 9 due to withdrawal of consent, 4 due to lack of efficacy at the highest tolerable dose, and 3 due to various other reasons).
- 81% (84/104) of patients achieved an effective dose of *FENTORA* during the open-label dose titration phase.
- During the double-blind treatment phase, 77 patients entered this period, 75 (71%) patients completed the double-blind phase, 2 (2%) patients withdrew during this period, and 73 patients were efficacy evaluable.
- No correlation was found between the effective dose of *FENTORA* and the dose of the ATC opioid taken during the study or average dose of rescue medication used prior to the study.

Efficacy

- Mean $SPID_{60}$ scores (primary efficacy measure) were significantly higher for *FENTORA* than placebo (8.3 vs. 3.6, respectively, $p<0.0001$).
- Significant differences in PID scores started at 10 minutes ($p<0.02$) and continued at all subsequent time points ($p<0.0001$) up to 120 minutes following *FENTORA* compared with placebo (see Figure 1 below).
- Mean PR scores were significantly higher following treatment with *FENTORA* than with placebo as early as 15 minutes ($p=0.0002$) and at all subsequent time points ($p<0.0001$) up to 120 minutes.

- Clinically significant (≥33%)[17] decreases in PI scores were greater for *FENTORA* (20%) versus placebo (11%) at 15 minutes ($p<0.01$) and at all subsequent time points through 120 minutes (65% for *FENTORA* vs. 28% for placebo, $p<0.0001$).
- A clinically significant (≥50%) improvement in PI was observed with FENTORA versus placebo at 30 minutes (30% vs. 13%, respectively, $p<0.01$) and at all subsequent time points through 120 minutes ($P<0.0001$).
- Patients experienced meaningful PR for more BTP episodes treated with *FENTORA* than for episodes in which placebo was administered (70% vs. 30%, respectively, $p<0.0001$). Meaningful PR was achieved by 30 minutes in 38% of BTP episodes treated with *FENTORA* vs. 16% for placebo.
- Patients receiving placebo were approximately 4 times as likely to use supplemental opioids for BTP episodes compared to those receiving *FENTORA* (risk ratio 0.22, 95% confidence interval (CI) 0.13-0.35).

Figure 1. Mean pain intensity difference (PID) over time (5-120 minutes)



In summary, approximately 80% of patients found an effective dose of *FENTORA* in the range of 100 mcg to 800 mcg. *FENTORA* was found to be efficacious compared to placebo, producing treatment differences across efficacy measures as early as 10 minutes after start of *FENTORA* administration, increasing through 60 minutes and maintained through 120 minutes, the last time point measured. Pain relief was significantly greater with *FENTORA* than with placebo occurring as early as 15 minutes following treatment with *FENTORA*.

Safety Profile

FENTORA was generally well tolerated in the dose range of 100 mcg to 800 mcg. Overall, AEs were reported by 65% (68/104) of patients. The most frequently occurring AEs during both the dose titration and double-blind treatment periods were nausea (19%), dizziness (13%), and somnolence (9%), dysguesia (8%), vomiting (6%), dry mouth (5%) which are typical of opioid side effects except for dysguesia.[13] Dysguesia was reported by patients as a bitter or bad taste of study drug. AEs were more likely to occur during the dose-titration phase (57%) than during the

double-blind phase (34%).[15] Serious adverse events (SAEs) were reported by two (2%) patients, of which one SAE was considered by the investigator to be possibly related to the study drug (accidental overdose with unresponsiveness to pain stimuli). The patient recovered after administration of oxygen.[13] The other SAE (diabetic gastroparesis) was considered not to be related to the study drug.[13] Both patients withdrew from the study due to these AEs and these SAEs resolved without residual effect. Ten additional patients discontinued the study due to AEs. Eleven of the 12 patients withdrew from the study during the dose-titration phase. Most of these AEs that led to study withdrawal were typical opioid side effects. Mild application site AEs were reported in 6 patients, of which only one patient discontinued due to an AE of gingival pain.[13] All application site AEs resolved without residual effect.

Study 2 – BTP Associated with Chronic Neuropathic Pain

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy and tolerability of *FENTORA* for the management of breakthrough pain in adult opioid-tolerant patients with chronic neuropathic pain.[18]

Eligible patients for this study were opioid-tolerant patients with a diagnosis of chronic neuropathic pain associated with diabetic peripheral neuropathy (30%), traumatic injury (23%), complex regional pain syndrome (18%), or postherpetic neuralgia (4%), resulting in functional disability of at least 3 months duration. In addition, patients experienced 1-4 BTP episodes per day with a duration of less than 4 hours for each BTP episode and were managed with stable doses of ATC opioid medications (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 mcg/hr, oxycodone ≥30 mg/day, oral hydromorphone ≥8 mg/day or an equianalgesic dose of another opioid, for 7 days or longer prior to enrollment into the study) for their persistent pain.

Key results from this placebo-controlled study 2 showed the following:

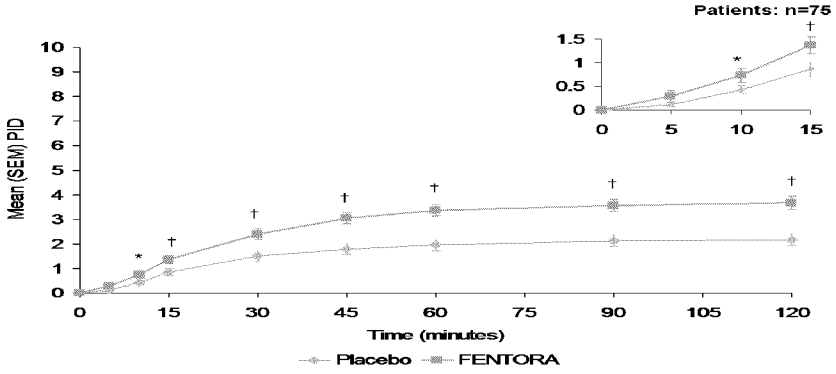
Patient Disposition

- The mean age of the patients in this study was 49 years, the majority were female (58%), and 92% were Caucasian.
- A total of 78% (80/102) of patients identified an effective dose between 100-800 mcg, 79 completed the dose-titration phase, 77 completed the double-blind phase and 75 patients were efficacy-evaluable.
- No correlation was found between the effective dose of *FENTORA* and the dose of the ATC opioid taken during the study or average dose of rescue medication used prior to the study.

Efficacy

- Mean $SPID_{60}$ scores (primary efficacy measure) were significantly higher for *FENTORA* than placebo (9.6 vs. 5.7, respectively, $p<0.0001$).
- Mean PID and PR scores were significantly higher with *FENTORA* than placebo at 10 minutes ($p<0.05$) and each subsequent time point at 15, 30, 45, 60, 90 and 120 minutes ($p<0.01$ for each time point). The magnitude of treatment differences, observed in mean PID and PR scores, continued to increase through 1 hour and was maintained through 2 hours (see Figure 2 below).
- Meaningful separation was seen as early as 15 minutes for clinically significant (≥33%) improvement and at 30 minutes for ≥50% improvement from baseline in PI for *FENTORA* vs. placebo.
- Patients experienced meaningful PR for more BTP episodes treated with *FENTORA* than for episodes in which placebo was administered (69% vs. 36%, respectively, $p<0.0001$. Meaningful PR was achieved by 30 minutes in 33% of BTP episodes treated with *FENTORA* vs. 15% for placebo.
- Global medication performance assessment ratings showed greater satisfaction with *FENTORA* than placebo at 60 and 120 minutes (2.1 vs. 1.2 and 2.2 vs. 1.3, respectively; $p<0.0001$ for both time points).
- Patients receiving placebo were nearly 4 times as likely to use supplemental opioids for BTP episodes compared to those receiving *FENTORA* (risk ratio 0.28, 95% CI 0.18-0.42).

Figure 2. Mean pain intensity difference (PID) over time (5-120 minutes)



* p<0.05 vs. placebo
† p<0.0001 vs. placebo

In summary, approximately 80% of patients found a successful dose of *FENTORA* in the range of 100 mcg to 800 mcg. *FENTORA* was found to be efficacious compared to placebo, producing treatment differences across efficacy measures as early as 10 minutes after start of *FENTORA* administration, increasing through 60 minutes and maintaining through 120 minutes, the last time point measured.

Safety Profile

FENTORA was generally well tolerated at doses of 100-800 mcg in this patient population. Overall, AEs were reported by 63% of patients. The most frequently occurring AEs were nausea (13%), dizziness (13%), and somnolence (10%); all of which are typical of opioid side effects. These AEs were more frequent during the dose-titration phase than during the double-blind treatment period (54% vs. 28%). Mild application site AEs were reported in 8 (8%) of patients, all of which resolved without residual effect. One patient experienced a serious adverse event (angina pectoris post coronary stent replacement) which was considered by the investigators to be unrelated to *FENTORA* and resolved without residual effect. This patient was withdrawn from the study. A total of twelve (12%) patients discontinued the study due to AEs, all of which occurred during the dose-titration period.

Open-label Safety Study (ongoing)

The long-term safety and tolerability of *FENTORA* in opioid-tolerant patients with BTP and chronic noncancer pain is being evaluated in an ongoing 18-month, open-label, multi-center study.[19,20,21,22]

Eligible patients for this study are opioid-tolerant patients with chronic noncancer pain (chronic low back pain, diabetic peripheral neuropathy, osteoarthritis, traumatic injury, chronic headache, or complex regional pain syndrome) who are experiencing 1-4 BTP episodes per day and are managed with ATC opioid medications (oral morphine ≥60 mg/day, or an equianalgesic dose of another opioid as ATC therapy, or transdermal fentanyl ≥50 mcg/hr, for 7 days or longer prior to enrollment into the study) for their persistent pain. This study is open to new patients (those naïve to *FENTORA*) and to patients who have completed 1 of 2 randomized double-blind *FENTORA* efficacy studies discussed above (Study 1 and Study 2). For new patients, the study consists of a screening visit, a dose-titration period and an 18-month open-label maintenance period. The effective dose for treatment naïve patients (100-800 mcg) was determined during the dose-titration period and was defined as the single dose strength of *FENTORA* that provided adequate analgesia (sufficient pain relief within 30 minutes) without unacceptable adverse events for the majority of BTP episodes. For patients who previously participated in either of the two double-blind studies, the study consists of only an 18-month maintenance treatment period at their previously identified effective dose.

The interim results are presented below:

Patient Exposure

Over 700 patients have been enrolled in this study, with over 400 patients treated with *FENTORA* longer than six months and over 200 patients treated for longer than one year.[19]

Mood, Functioning and Quality of Life

A 3-month interim analysis, involving 337 patients, was conducted to evaluate the impact of *FENTORA* on mood, functioning and quality of life in this ongoing, open-label, long-term safety study.[21] Preliminary results from this 3-month analysis demonstrated that patients treated with *FENTORA* showed trends toward improvements from baseline to 3 months in the majority of mood, functioning and quality of life measurements (based on changes in the 36-item Short-Form Health Survey (SF-36) and Profile of Mood States (POMS)).

Patient Preference Assessment

A 3-month interim analysis was conducted to evaluate the overall performance and patient preference of FENTORA relative to that of the patients' previous BTP therapy in this open-label safety study.[22] Interim results, in which 406 patients were enrolled and 337 patients met the analysis inclusion criteria, are as follows:

- Most commonly reported primary pain condition at baseline was chronic low back pain in 60% of patients.
- The mean age of the patients in this study was 48 years, the majority were female (56%), and 95% were Caucasian.
- A total of 87% (354/406) of patients identified an effective dose of *FENTORA* to adequately treat BTP, 13% did not find an effective dose or were ongoing in their titration at the time of this analysis.
- The majority of patients (93%) rated the global medication performance of *FENTORA* to be "good", "very good" or "excellent" for the management of their BTP.
- The majority of patients (91%) preferred *FENTORA* to their previously used rescue medication.
- Most patients reported that *FENTORA* provided a faster onset of relief than their previous rescue medication (95%), was easier to administer (74%), and was more convenient to use (70%) than their previous medications used for rescue.

Safety Profile

Interim safety data is available for 94 patients.[20] *FENTORA* was generally well tolerated in the dose range of 100 mcg to 800 mcg with a relatively low incidence of AEs (23%). There were no reports of respiratory depression or death. The most common AEs that occurred in the 94 patients were nausea (7%), dizziness (5%), back pain (4%), headache (4%), dyspepsia (3%), application site pain (2%), arthralgia (2%), and anxiety (2%). Four patients reported oral mucosal AEs (pain, irritation, ulceration, or vesicles) associated with tablet application site which resolved within 1-15 days for 3 patients. The resolution time for the fourth patient was unknown.

In summary, to date, *FENTORA* has been well tolerated at doses ranging from 100 to 800 mcg for the management of BTP in opioid-tolerant patients with noncancer chronic pain. Based on this interim analysis, the majority of patients in this study preferred *FENTORA* compared to their previously used rescue medication.

General Considerations

- The initial dose of *FENTORA* should be 100 mcg. For patients switching from oral fentanyl products including Actiq® (oral transmucosal fentanyl citrate) or OTFC to *FENTORA*, please refer to the dosing conversion recommendation table in the **Dosage and Administration** section of the *FENTORA* prescribing information.

- *FENTORA* should be individually titrated to a dose that provides adequate analgesia with tolerable side effects.

- The successful dose of *FENTORA* cannot be predicted by the daily maintenance dose of the opioid used to treat persistent pain or the dose of previously used rescue medication. Therefore, the optimal dose of *FENTORA* should be determined by dose titration, starting at a relatively low dose.

In conclusion, treatment with *FENTORA* was generally well tolerated at doses of 100 mcg through 800 mcg for the management of BTP in opioid-tolerant patients with noncancer chronic pain. Approximately 80% of the patients titrated to a successful dose of *FENTORA* in two randomized, double-blind, placebo-controlled studies conducted in patients with BTP associated with chronic low back pain and in chronic neuropathic pain. *FENTORA* was found to be efficacious compared to placebo, producing analgesic effects as early as 10 minutes after start of *FENTORA* administration, increasing through 60 minutes and maintained through 120 minutes, the last time point measured. Cephalon makes no recommendation for use of *FENTORA* beyond the indication in the FDA-approved product labeling.

As noted in the cover letter, *FENTORA* is indicated "for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. *FENTORA* **must not** be used in opioid non-tolerant patients."

---

[1] FENTORA™ (fentanyl buccal tablet) [current approved prescribing information]. Frazer, PA: Cephalon, Inc.

[2] Portenoy RK, Hagen NA. Breakthrough pain: Definition and manifestations. *Primary Care & Cancer* April: 27-33, 1991.

[3] Portenoy RK, Hagen NA. Breakthrough pain: Definition, prevalence and characteristics. *Pain* 41: 273-281, 1990.

[4] Portenoy RK, Payne D, Jacobsen P, et al. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain* 81: 129-134, 1999.

[5] Bennett D, et al. Consensus panel recommendations for the assessment and management of breakthrough pain – Part 1 assessment. *P&T*. 30: 296-301, 2005.

[6] Zeppetalla G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. *J Pain Symptom Manage.* 20: 87-92, 2000.

[7] Portenoy RK, Bennett DS, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain* 7(8): 583-591, 2006.

[8] Zeppetalla G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in patients with non-malignant terminal disease admitted to a hospice. *Palliative Med.* 15(3): 243, 2001.

[9] Pather SI, Siebert JM, Hontz J, et al. Enhanced buccal delivery of fentanyl using the OraVescent drug delivery system. *Drug Delivery Tech.* 1:54-57, 2001.

[10] Durfee S, Messina J, Khankari R. Fentanyl effervescent buccal tablets: enhanced buccal absorption. *American Journal of Drug Delivery*: 4:1-5, 2006.

[11] Portenoy RK, Taylor D, Messina J, et al. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain.* 22 (9):805-811, 2006.

[12] Taylor D, Portenoy R, Messina J, et al. A randomized, placebo-controlled study of fentanyl effervescent buccal tablets for relief of breakthrough pain in opioid-tolerant patients with cancer. *The Journal of Pain.* 7 (Suppl 1):2, 2006. (abstract)

[13] Portenoy R, Messina J, Xie F, et al. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin.* 23(1): 223-233, 2007.

[14] Portenoy R, Messina J, Xie F, et al. Fentanyl buccal tablet (FBT) for the treatment of breakthrough pain in opioid-treated patients with chronic low back pain: A randomized, placebo-controlled study. [Poster presentation]. Presented at the American Society of Regional Anesthesia and Pain Medicine (ASRA) Pain Medicine Meeting and Workshops, San Francisco, CA, November 16-19, 2006.

[15] Portenoy R, Xie F, Messina J, et al. Fentanyl buccal tablet (FBT) for the treatment of breakthrough pain in opioid-treated patients with chronic low back pain: A randomized, placebo-controlled study. [abstract] *Reg Anesth Pain Med.* 30(3): A-13, 2006.

[16] Data on file (fentanyl buccal tablet Clinical Study Report C25608/3042/BP/US). Frazer, PA: Cephalon, Inc., 2006.

[17] Farar JT, Portenoy R, Berlin JA, et al. Defining the clinically important pain outcome measures. *Pain* 88:287-294, 2000.

[18] Data on file (fentanyl buccal tablet Clinical Study Report C25608/3041/BP/US). Frazer, PA: Cephalon, Inc., 2006.

[19] Data on file (fentanyl buccal tablet Clinical Study Report C25608/3040/BP/US). Frazer, PA: Cephalon, Inc., 2006.

[20] Hale M, Webster L, Peppin J, et al. Open-label study of fentanyl effervescent buccal tablets in patients with chronic pain and breakthrough pain: Interim safety and tolerability results. [Poster presentation]. Presented at the American Academy of Pain Medicine's Annual Meeting, San Diego, CA, February 22-25, 2006.

[21] Nalamachu S, Xie F, Messina J, et al. Impact of fentanyl buccal tablet (FBT) on mood, functioning, and quality of life in patients with breakthrough pain. [Poster presentation]. Presented at the American Academy of Phyical Medicine and Rehabilitation. 67th Annual Assembly and Technical Exhibition, Honolulu, HI, November 9-12, 2006.

[22] Nalamachu S, Xie F, Messina J, et al. Evaluation of patient preference for fentanyl buccal tablet (FBT) to manage breakthrough pain. [Poster presentation]. Presented at the American Academy of Phyical Medicine and Rehabilitation. 67th Annual Assembly and Technical Exhibition, Honolulu, HI, November 9-12, 2006.

Enclosures: Reference 1.

FENT014 /AS 01-2007