March 4, 2011

Wayne Anderson, M.D.
45 Castro Street
Suite 225
San Francisco, CA 94114

Dear Dr. Anderson:

Your Cephalon Sales Specialist Brian Endicott has forwarded your request for medical information regarding FENTORA® (fentanyl buccal tablet) [C-II]. In response to your inquiry we have enclosed the following medical information:

• Use for the Management ofBreakthrough Pain in Opioid-tolerant Patients with Chronic Low Back Pain.

Thank you for your interest in this Cephalon, Inc. product. We have enclosed a copy of the full prescribing information for your review. Cephalon does not recommend the use of this product beyond its FDA approved product labeling.

If you have any questions concerning the information provided or require any further assistance, please contact Cephalon Medical Information at (800) 896-5855 or via e-mail at USMedInfo@Cephalon.com.

Sincerely,
<Signature>

Medical Information Department
Medical Affairs
Cephalon, Inc.

IRMS: 381132

Enclosures: FENTORA Prescribing Information

Use of FENTORA® (fentanyl buccal tablet) [C-II] for the Management of Breakthrough Pain in Opioid Tolerant Patients with Chronic Low Back Pain

FENTORA is not FDA-approved for the management of breakthrough pain (BTP) in patients with chronic low back pain. However, clinical studies evaluating the use of FENTORA for the management of breakthrough pain in opioid tolerant patients with chronic noncancer pain conditions have been conducted. A summary of these data is presented below for your review.

Clinical Studies

Randomized, Double-blind, Placebo-controlled Study

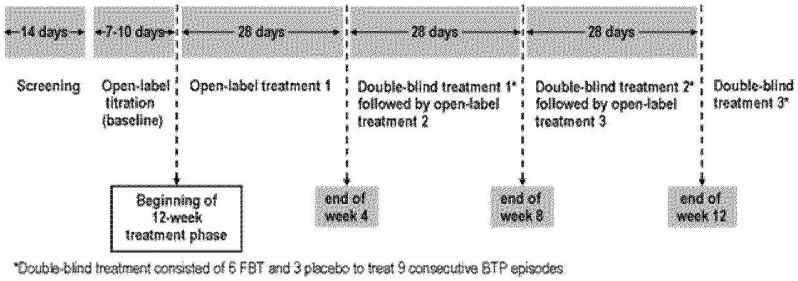
In a short-term study that enrolled opioid tolerant patients with chronic low back pain and BTP, FENTORA was found to be efficacious compared to placebo, producing a significantly greater reduction in pain intensity as early as 10 minutes after tablet administration through 120 minutes, the last time point measured. Pain relief was significantly greater with FENTORA than with placebo occurring as early as 15 minutes and at all subsequent time points through 120 minutes. Inclusion and exclusion criteria were similar to the pivotal study discussed below.[1] The overall adverse event (AE) profile of FENTORA in this study was consistent with potent opioid use in a non-cancer population. One reported serious adverse event (SAE) was considered by the investigator to be possibly related to the study drug (accidental overdose with unresponsiveness to pain stimuli; patient fully recovered).[2]

Randomized, Double-blind, Placebo-controlled, Open-label Study

A 12-week multicenter, open-label study with 3 within-patient, randomized, double-blind placebo-controlled treatment periods was conducted to evaluate the efficacy and safety of FENTORA for the management of noncancer-related BTP in opioid tolerant patients.[3]

Eligible patients experienced, on average, 1 - 4 BTP episodes per day while being managed on stable doses of around-the-clock (ATC) opioid medications (ie, on either $\geq$ 60 mg/day oral morphine, $\geq$ 25 mcg/hr transdermal fentanyl, $\geq$ 30 mg/day oxycodone, $\geq$ 8 mg/day hydromorphone, or an equianalgesic dose of another opioid daily) taken for more than 30 days prior to study enrollment. Patients were receiving short-acting opioids for breakthrough pain with partial relief. Patients also had to have a baseline pain intensity score of $\leq$ 6 over the 24 hours before enrollment. Patients were excluded if they had a recent history of alcohol or other substance abuse and if they had headache pain.[4] Patients entered the initial open-label dose titration phase to identify a successful dose of FENTORA, defined as the single dose of 100-800 mcg that provided adequate pain relief for at least 2 of 3 BTP episodes without unacceptable adverse events (AEs). Patients served as their own controls during the double-blind treatment periods (Figure 1).

Figure 1. Study Design



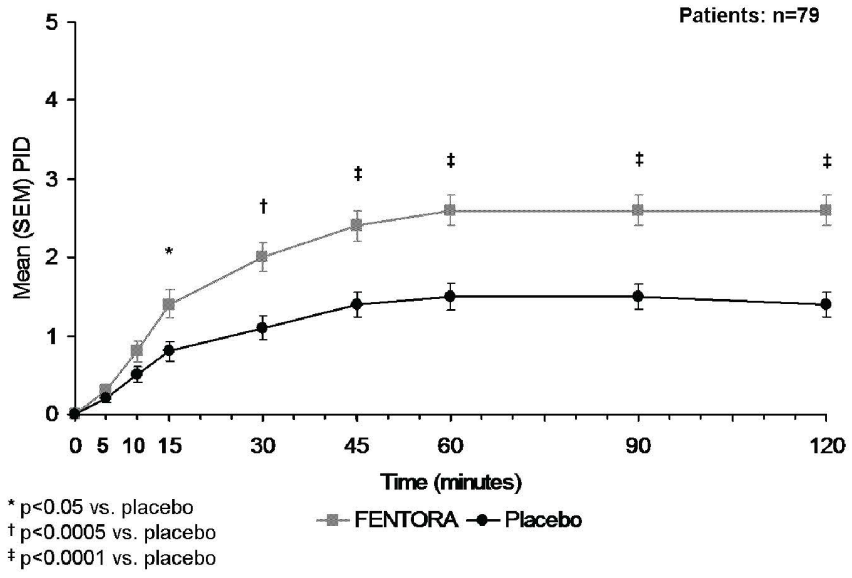
Key findings from this study showed the following patient demographics and patient disposition.[3] The mean age of the patients in this study was 52 years; the majority were Caucasian (94%) and 62% were female. There were 70 (47%) patients in this study with a primary back pain condition.

At baseline, the most common (≥ 10%) ATC opioid medications used were fentanyl (29%), oxycodone (27%), morphine (25%), and methadone (14%). The median oral morphine equivalent ATC dose in patients (n = 95) taking oral opioids was 130.0 mg/day (range 40 mg to 1500 mg). At baseline, the most common (≥ 10%) rescue medications used were oxycodone (43%), hydrocodone (37%), and morphine (11%). The median oral morphine equivalent rescue medication for BTP in patients taking oral opioids was 16.0 mg/BTP episode (range 3.8 mg to 60 mg). Out of 199 patients that were screened for the study, 148 enrolled in the study received at least 1 dose of FENTORA and were evaluated for safety.

Out of 148, 105 (71%) patients achieved a successful dose of FENTORA during the titration phase, and 104 entered the post-titration period. There were 45 out of 148 (30%) patients that discontinued the titration phase, primarily due to lack of efficacy (n = 19) and AEs (n = 9). A total of 79 patients in the third double-blind treatment period were evaluable for analysis of the primary efficacy variable.

After 12 weeks of treatment (double-blind treatment period 3), the mean sum of pain intensity difference $SPID_{60}$ (primary efficacy measure) was significantly greater for FENTORA than placebo (7.7 vs 4.6, $P < 0.0001$). Mean PID scores (Figure 2) were significantly greater following FENTORA administration compared with placebo, occurred as early as 15 minutes ($P < 0.05$), and continued at all subsequent time points up to 120 minutes ($P < 0.0001$). PI improved by ≥ 33% and ≥ 50% at 5 minutes and 15 minutes, respectively, following drug administration and continuing through 120 minutes. This improvement was significantly greater following episodes treated with FENTORA compared to placebo. For meaningful pain relief, statistically significant separation in favor of FENTORA was observed at 10 minutes for 14% of episodes in patients who took FENTORA compared with 7% of episodes in patients who took placebo. The study also concluded that mean pain relief (PR) scores were higher following treatment with FENTORA than with placebo after 5 minutes ($P = 0.0013$), and the scores were maintained through 2 hours ($P < 0.0001$).[3]

Figure 2. Pain Intensity Difference (PID) for BTP Episodes during Double-Blind Treatment 3



An analysis evaluated the effect of FENTORA on daily functioning in opioid tolerant patients with noncancer-related BTP. The assessment measures were Brief Pain Inventory – Interference Scale (BPI-IS), Goal Attainment Scale (GAS), Patient's Assessment of Functioning (PAF), and Clinician's Assessment of Patient Functioning (CAPF). Overall, functioning numerically improved across all components as measured by the GAS, PAF, and CAPF. Thirty to forty percent of patients were much improved/very much improved from baseline on these measures. However, no change was seen in the BPI-IS.[5]

FENTORA was generally well-tolerated in the dose range of 100 mcg to 800 mcg. The most frequently occurring adverse events were generally typical of opioid treatment, such as nausea (10% dose titration, 10% post-titration), dizziness (9% dose titration), and somnolence (8% post-titration). Thirteen (9%) patients had adverse events associated with the table application site, of which erythema was the most commonly reported (n = 6) application site AE. A total of 15 (10%) patients discontinued the study due to AEs, nausea and headache being the most common reason. Ten (7%) patients experienced SAEs; 2 were related to study drug (multiple-drug overdose and pneumonia [n = 1] and opioid abuse [n = 1]). Other SAEs included bronchiolitis obliterans, pneumonia, pyelonephritis, infections, osteomyelitis, panic attack, biliary dilatation, and neuropathic pain. There were no reports of deaths in this study.[3]

Randomized, Double-blind, Crossover Study – FENTORA vs Oxycodone Immediate-Release

In a 2 x 2 crossover study, opioid tolerant patients with a ≥ 3 month history of chronic pain were randomized to the order of open-label titration with FENTORA (200, 400, 600, 800 mcg) and oxycodone immediate-release (Oxy IR, 15, 30, 45, 60 mg) for the management of BTP.[6,7] Following titration to a successful dose of both study drugs, patients entered the DB phase and were randomized to treatment for 10 BTP episodes with 1 of the previously identified successful

doses of study drug followed by crossover to treatment for 10 BTP episodes with the alternative study drug. The primary efficacy measure was pain intensity difference 15 minutes after administration of study drug (PID_{15}). Other efficacy measures included PID at other time points postdose (5 through 60 minutes), pain relief (5 through 60 minutes), proportion of BTP episodes for which patients experienced a meaningful reduction in pain intensity, medication performance assessment, and patient preference for BTP medication. Adverse events (AEs) were also recorded.

Of the 323 patients enrolled in the study, the mean age was 50.2 years (range 21 to 76 years), 58% were female, 92% were white, and the most common primary painful condition was back pain (58%).[6,7] Two hundred three (63%) patients achieved a successful dose of both study drugs, 191 (59%) completed the titration phase, and 180 (56%) completed the DB phase. The primary efficacy variable, the mean PID_{15}, showed a statistically significant difference in favor of FENTORA over Oxy IR for alleviating BTP (LS mean [SE] 0.82 [0.07] vs 0.59 [0.07], respectively; $P < 0.0001$). Secondary efficacy measures favored FBT and showed significant differences versus Oxy IR from 5 minutes postdose for PID and 10 minutes postdose for pain relief. The proportion of episodes with a $\geq 33\%$ improvement in pain intensity was significantly greater for episodes treated with FENTORA compared to Oxy IR beginning at 15 minutes and continuing through 45 minutes postdose ($P < 0.05$). More patients (52%) preferred FENTORA than Oxy IR (33%) for management of BTP. Both study drugs were generally well-tolerated, reported AEs were typical of those observed with opioids, and the majority occurred during titration. FENTORA was generally well-tolerated at the site of tablet placement. Ten percent of patients reported application site AEs, 91% of these events resolved with no residual effect, none changed in severity, and 3 (< 1%) patients discontinued due to these events. Two serious adverse events (pneumonia) were reported in 1 patient; both occurrences were considered unrelated to study drug. With the exclusion of 1 patient who died between screening and enrollment (patient was not treated with either study drug), no other patient deaths occurred during this study.

Open-label Safety Study in Chronic Noncancer Pain Conditions

The long-term safety and tolerability of FENTORA in opioid tolerant patients with BTP and chronic noncancer pain conditions was evaluated in an 18-month, open-label, multicenter study.[8,9] There were 416 out of a total of 728 (57%) patients that had chronic low back pain as their primary etiology. Adverse event data was analyzed from the 728 patients (588 new and 140 rollover patients, and FENTORA at doses of 100 to 800 mcg was generally well-tolerated. The most frequently occurring adverse events overall ($\geq 5\%$ of patients) were nausea (23%); back pain (14%); vomiting (14%); headache (12%); constipation, dizziness, and somnolence (each 9%); urinary tract infection, arthralgia, and pain in extremity (each 8%); diarrhea, peripheral edema, and depression (each 7%); sinusitis, upper respiratory tract infection, nasopharyngitis, bronchitis, anxiety, and insomnia (each 6%) and fatigue, contusion, and hyperhidrosis (each 5%). Adverse events associated with the tablet application site occurred in 94 (13%) patients: pain, irritation, and ulcer being common. A total of 108 (15%) patients withdrew from the study due to at least one AE. A total of 17% patients displayed at least 1 aberrant behavior, out of which 11% (n = 124) had an aberrant behavior related to the use of FENTORA.[10] Serious adverse

events were reported in 119 (16%) patients, and those associated with respiratory function were observed in 11 (2%) patients. All reported deaths (n = 6) were considered by the investigators not related or unlikely to be related to treatment with study drug. However, there was 1 additional report of death, of which was considered possibly related to study drug overdose, involving a family member of a patient enrolled in the study.[8,9]

Summary

FENTORA is not FDA-approved for the management of BTP in patients with chronic low back pain. However clinical studies have evaluated the use of FENTORA in the management of BTP in opioid tolerant patients with chronic low back pain, and the results of these studies have been published. All of the studies evaluating the efficacy of FENTORA for the management of noncancer-related BTP met their primary efficacy endpoint. Cephalon does not recommend the use of FENTORA outside its FDA-approved product label.

For prescribing information, including the boxed warning, please see the enclosed package insert for FENTORA.

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1. Portenoy RK, Messina J, Xie F, Peppin J. 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.* 2007; 23(1):223-233.

2. Portenoy RK, Messina J, Xie F, Peppin J. 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.* 2007; 23(1):223-233.

3. Farrar JT, Michna E, Messina J. Fentanyl buccal tablet (FBT) in opioid-tolerant patients with non-cancer-related breakthrough pain on around-the-clock opioids: A 12-week study using a novel double-blind, placebo-controlled design. *Pain Medicine.* 2008; 9(1):102.

4. Data on file (fentanyl buccal tablet Clinical Study Report C25608/3052/BP/US). Frazer, PA: Cephalon, Inc.

5. Farrar JT, Michna E, Messina J, Xie F Impact of Fentanyl Buccal Tablet on Both Patient and Clinician Ratings of Functioning in Patients with Breakthrough Pain. [Poster Presentation]. Presented at 27th Annual Scientific Meeting of the American Pain Society, Tampa, FL, May 8-10, 2008.

6. Data on file (fentanyl buccal tablet Clinical Study Report C25608/3055/BP/US). Frazer, PA: Cephalon, Inc.

7. Ashburn MA, Messina J, Xie F. Efficacy and Safety of Fentanyl Buccal Tablet Compared with Immediate-Release Oxycodone for the Management of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain. [abstract]. Presented at the Amercian Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX, February 3-6, 2010.

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

9. Fine P, Rathmell JP, Messina J, Xie F Long-Term Safety Profile of Fentanyl Buccal Tablets in Opioid-Tolerant Patients with Chronic Noncancer Pain and Breakthrough Pain. [Poster Presentation]. Presented at 12th World Congress on Pain of the International Association for the Study of Pain, Glasgow, Scotland, August 17-22, 2008.

10. Passik S, Messina J, Golsorkhi A, Xie F What can we learn about aberrant drug-related behavior from a large clinical trials database of patients with chronic pain managed by opioids? [Poster Presentation]. Presented at 8th International Conference on Pain and Chemical Dependency (ICPCD), Philadelphia, PA, October 29 - November 1, 2008.

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