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CII

FENTORA™
(Fentanyl buccal tablet)
Each tablet contains fentanyl citrate equivalent to fentanyl base: 100, 200, 400, 600 and 800 mcg

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

***FENTORA* contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. *FENTORA* can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing *FENTORA* in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.**

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

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is **contraindicated** in the management of acute or postoperative pain. **This product is not indicated for use in opioid non-tolerant patients**.

Patients and their caregivers must be instructed that *FENTORA* 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.)

Due to the higher bioavailability of fentanyl in *FENTORA*, when converting patients from other oral fentanyl products, including oral transmucosal fentanyl citrate (OTFC and Actiq®), to *FENTORA*, do not substitute *FENTORA* on a mcg per mcg basis. Adjust doses as appropriate (see DOSAGE AND ADMINISTRATION).

***FENTORA* is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.**

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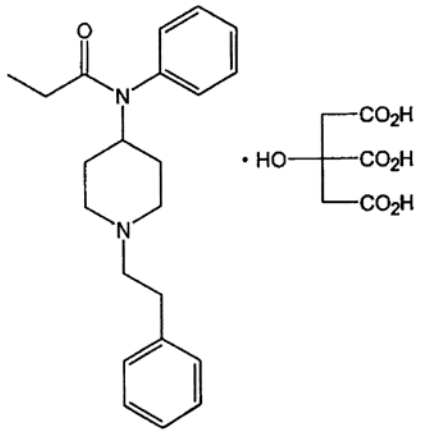
DESCRIPTION

FENTORA (fentanyl buccal tablet) is a potent opioid analgesic, intended for buccal mucosal administration. *FENTORA* is formulated as a flat-faced, round, beveled-edge tablet.

FENTORA is designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

FENTORA employs the OraVescent® drug delivery technology, utilizing an effervescent reaction which is thought 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).

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100-microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacology:

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory

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depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia
The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *FENTORA* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Central Nervous system
The precise mechanism of the analgesic action is unknown although fentanyl is known to be a mu opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System
Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid induced-effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

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Cardiovascular System
Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System
All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of another oral transmucosal fentanyl citrate (Actiq). Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.
(See BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.)

PHARMACOKINETICS
Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of *FENTORA* increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption:
Following buccal administration of *FENTORA*, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of *FENTORA* is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and

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becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of *FENTORA* and Actiq (oral transmucosal fentanyl citrate [OTFC]), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with *FENTORA*) (Table 1).

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

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

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

Similarly, in another bioavailability study exposure following administration of *FENTORA* was also greater (approximately 50%) compared to Actiq (OTFC).

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl were substantially greater with *FENTORA* compared to Actiq (OTFC) (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another (see **DOSAGE and ADMINISTRATION**). Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for *FENTORA*.

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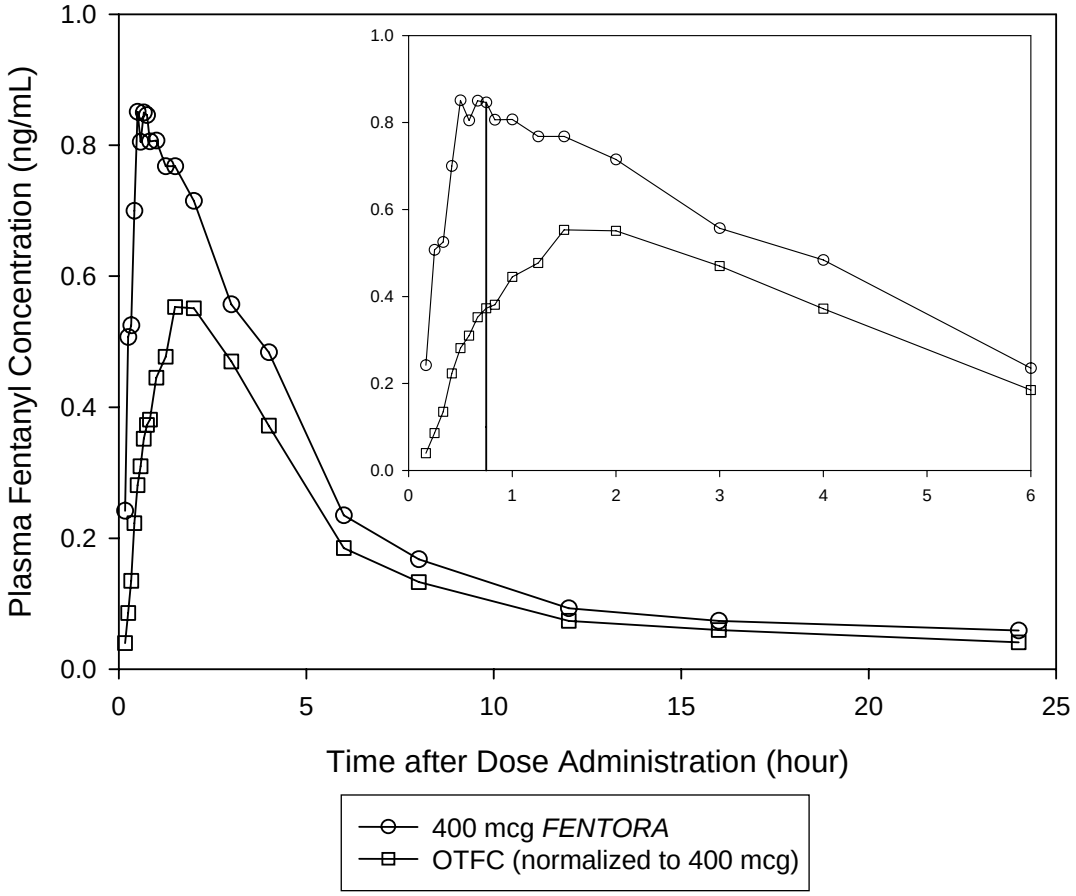
Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of *FENTORA* and Actiq(OTFC) in Healthy Subjects



Actiq (OTFC) data was dose adjusted (800 mcg to 400 mcg).

Systemic exposure to fentanyl following administration of *FENTORA* increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range. Mean pharmacokinetic parameters are presented in Table 2. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 2: Pharmacokinetic Parameters* Following Single 100-, 200-, 400-, and 800-mcg Doses of *FENTORA* in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25±0.14	0.40±0.18	0.97±0.53	1.59±0.90

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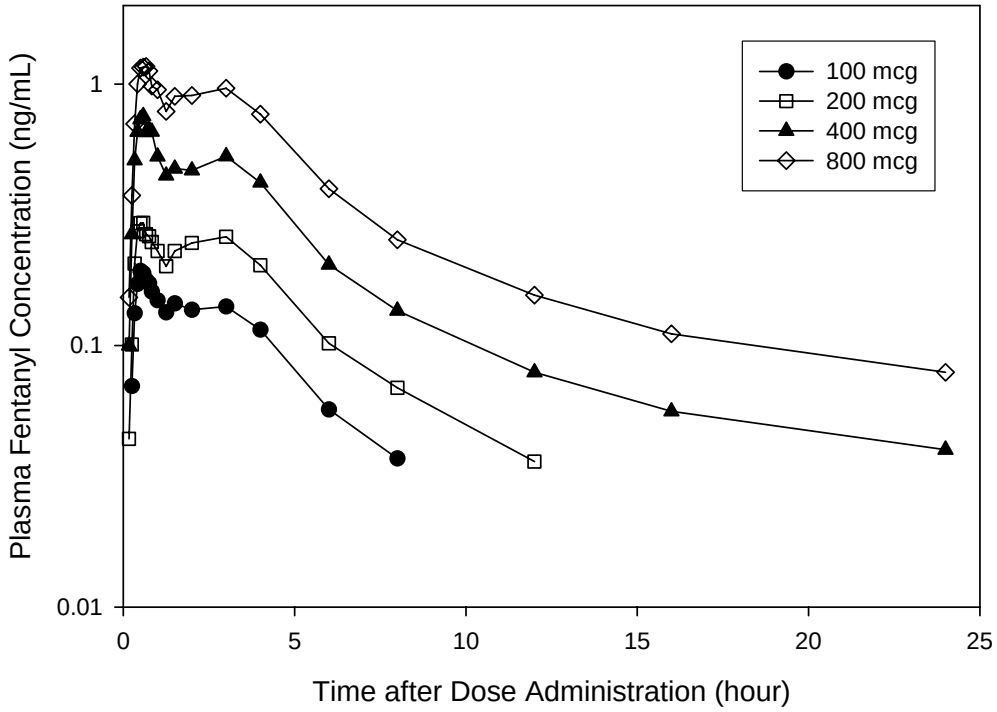
T_{max}, minute (range)**	45.0 (25.0-181.0)	40.0 (20.0-180.0)	35.0 (20.0-180.0)	40.0 (25.0-180.0)
$AUC_{0\text{-}inf}$ (ng/mL)	0.98±0.37	2.11±1.13	4.72±1.95	9.05±3.72
$AUC_{0\text{-}tmax}$ (ng/mL)	0.09±0.06	0.13±0.09	0.34±0.23	0.52±0.38
T1/2, hr**	2.63 (1.47-13.57)	4.43 (1.85-20.76)	11.09 (4.63-20.59)	11.70 (4.63-28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Figure 2: Mean Plasma Concentration Versus Time Profiles Following Single 100-, 200-, 400-, and 800-mcg Doses of *FENTORA* in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of *FENTORA* was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200-mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 4.

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Table 4. Pharmacokinetic Parameters in Patients with Mucositis.

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng-hr/mL)	$AUC_{0\text{-}8}$ (ng-hr/mL)
Mucositis	1.25±0.78	25.0 (15-45)	0.21±0.16	2.33±0.93
No mucositis	1.24±0.77	22.5 (10-121)	0.25±0.24	1.86±0.86

Distribution:
Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Metabolism:
The metabolic pathways following buccal administration of *FENTORA* have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active. (see **PRECAUTIONS: Drug Interactions** for additional information).

Elimination:
Disposition of fentanyl following buccal administration of *FENTORA* has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

Special Populations:
The pharmacokinetics of *FENTORA* has not been studied in Special Populations.

Race
The pharmacokinetic effects of race with the use of *FENTORA* have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to US subjects (57.4 kg versus 73kg).

Age
The effect of age on the pharmacokinetics of *FENTORA* has not been studied.

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Gender
Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Renal or Hepatic Impairment:
The effect of renal or hepatic impairment on the pharmacokinetics of *FENTORA* has not been studied. Although fentanyl kinetics are known to be altered as a result of hepatic and renal disease due to alterations in metabolic clearance and plasma protein binding, the duration of effect for the initial dose of fentanyl is largely determined by the rate of distribution of the drug.

Diminished metabolic clearance may, therefore, become significant, primarily with repeated dosing or at very high single doses. For these reasons, while it is recommended that *FENTORA* is titrated to clinical effect for all patients, special care should be taken in patients with severe hepatic or renal disease (See **PRECAUTIONS**).

Drug interactions
The interaction between ritonavir and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52%-420%) increase in fentanyl $AUC_{0-\infty}$. Coadministration of ritonavir in patients receiving *FENTORA* has not been studied; however, an increase in fentanyl AUC is expected. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**.)

CLINICAL TRIALS

Breakthrough Pain:
The efficacy of *FENTORA* was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of *FENTORA*. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of *FENTORA* and 3 being placebo. Patients used one tablet (either *FENTORA* or Placebo) per breakthrough pain episode.

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Patients assessed pain intensity on a scale that rated the pain as scale 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was measured at 15, 30, 45 and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

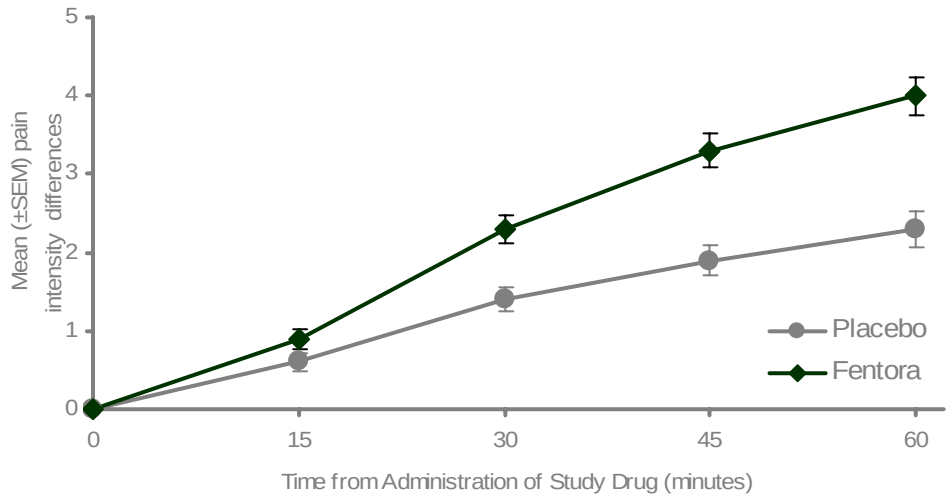
Sixty five percent of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 3. The median dose was 400 mcg.

Table 3.
Successful Dose of *FENTORA* Following Initial Titration

FENTORA Dose	(N=80) n (%)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for *FENTORA*-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18) ($p<0.0001$).

Mean Pain Intensity Difference (PID) at Each Time Point During the Double-Blind Treatment Period



*p<0.01 *FENTORA* versus placebo, in favor of *FENTORA*, by one-sample Wilcoxon signed rank test
†p<0.0001 *FENTORA* versus placebo, in favor of *FENTORA*, by one-sample Wilcoxon signed rank test
PID=pain intensity difference; *FENTORA* fentanyl; SEM=standard error of the mean

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INDICATIONS AND USAGE
(See BOXED WARNING and CONTRAINDICATIONS)
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 at least 60 mg of oral morphine/day, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not on a chronic regimen of opiates. For this reason, *FENTORA* is contraindicated in the management of acute or postoperative pain.

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

CONTRAINDICATIONS

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, *FENTORA* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

FENTORA is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

WARNINGS
See BOXED WARNING
The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors), and alcoholic beverages may produce increased depressant effects. Hypoventilation, hypotension, and profound sedation may occur.

FENTORA is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Pediatric Use: The safety and efficacy of *FENTORA* have not been established in pediatric patients below the age of 18 years.

Patients and their caregivers must be instructed that *FENTORA* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children. (See **SAFETY AND**

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HANDLING, **PRECAUTIONS**, and **MEDICATION GUIDE** for specific patient instructions.)

Drug Abuse, Addiction and Diversion of Opioids
FENTORA contains fentanyl, a mu -opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse, and criminal diversion.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since *FENTORA* tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

FENTORA should be handled appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Physical Dependence and Withdrawal
The administration of *FENTORA* should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient

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with cancer and chronic pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

Respiratory Depression
Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in *FENTORA*. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

PRECAUTIONS
General
The extent of fentanyl absorption with different formulations of transmucosal delivery systems can be substantially different; therefore, the same dose of fentanyl in two different formulations should not be viewed as equivalent. Therefore, caution must be exercised when switching patients from one product to another (See **DOSAGE and ADMINISTRATION**).

For patients not previously using oral transmucosal fentanyl citrate, the initial dose of *FENTORA* should be 100-mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *FENTORA* should be warned of these dangers and should be counseled accordingly.

The use of concomitant CNS active drugs requires special patient care and observation. (See **WARNINGS**.)

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Chronic Pulmonary Disease
Because potent opioids can cause respiratory depression, *FENTORA* should be titrated with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of *FENTORA* may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure
FENTORA should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

Application Site Reactions
In clinical trials, 10% of all patients exposed to *FENTORA* reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment, were self-limited and only resulted in treatment discontinuation for 2% of patients.

Cardiac Disease
Intravenous fentanyl may produce bradycardia. Therefore, *FENTORA* should be used with caution in patients with bradyarrhythmias.

Hepatic or Renal Disease
Insufficient information exists to make recommendations regarding the use of *FENTORA*® in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Information for Patients and Their Caregivers

1. **Patients and their caregivers must be instructed that children, especially small children, exposed to *FENTORA* are at high risk of FATAL RESPIRATORY DEPRESSION**. Patients and their caregivers must be instructed to keep *FENTORA* tablets out of the reach of children. (See **SAFETY AND HANDLING, WARNINGS**, and **MEDICATION GUIDE** for specific patient instructions.)
2. Patients and their caregivers should be provided a Medication Guide each time *FENTORA* is dispensed because new information may be available.
3. Patients should be aware that *FENTORA* contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
4. Patients should be instructed that the active ingredient in *FENTORA,* fentanyl, is a drug that some people abuse. *FENTORA* should be taken only by the patient it was

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prescribed for, and it should be protected from theft or misuse in the work or home environment.

5. Patients should be instructed that *FENTORA* tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. They are to be placed between the cheek and gum above a molar tooth and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
6. Patients should be cautioned to talk to their doctor if breakthrough pain is not alleviated or worsens after taking *FENTORA*.
7. Patients should be cautioned that *FENTORA* can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Patients taking *FENTORA* should be warned of these dangers and counseled accordingly.
8. Patients should be warned to not combine *FENTORA* with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
9. Female patients should be informed that if they become pregnant or plan to become pregnant during treatment with *FENTORA,* they should ask their doctor about the effects that *FENTORA* (or any medicine) may have on them and their unborn children.
10. Patients and caregivers should be advised that if they have been receiving treatment with *FENTORA* and the medicine is no longer needed they should contact Cephalon at 1-800-896-5855 or flush any remaining product down the toilet.
11. Patients should be warned that the active ingredient in *FENTORA* is fentanyl which is a drug that some people abuse. *FENTORA* should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.

Disposal of Unopened *FENTORA* Blister Packages When No Longer Needed
Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused *FENTORA,* remove *FENTORA* tablets from blister packages and flush down the toilet. Do not flush the *FENTORA* blister packages or cartons down the toilet. (See **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *FENTORA* are provided in the *FENTORA* Medication Guide. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, they should be instructed to call the toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

Laboratory Tests
The effects of *FENTORA* on laboratory tests have not been evaluated.

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Drug Interactions

See **WARNINGS.**

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when *FENTORA* is given concurrently with agents that affect CYP3A4 activity. Coadminstration with agents that induce 3A4 activity may reduce the efficacy of *FENTORA*. The concomitant use of *FENTORA* with ritonavir or other strong 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazadone may result in a potentially dangerous increase in fentanyl plasma concentrations The concomitant use of moderate CYP3A4 inhibitors such as amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil with *FENTORA* may also result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving *FENTORA* and potent and moderate CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage increase should be done conservatively. (See **PHARMACOKINETICS, Drug interactions** and **DOSAGE AND ADMINISTRATION**) .

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. tymphimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl impairs fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for *FENTORA*.

Pregnancy - Category C
There are no adequate and well-controlled studies in pregnant women. *FENTORA* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl.

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Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for *FENTORA*.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m^2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

Labor and Delivery
Fentanyl readily passes across the placenta to the fetus; therefore *FENTORA* is not recommended for analgesia during labor and delivery.

Nursing Mothers
Fentanyl is excreted in human milk; therefore *FENTORA* should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using *FENTORA*.

Pediatric Use
See WARNINGS.

Geriatric Use
Of the 304 patients with cancer in clinical studies of *FENTORA* 69 (23%) were 65 years of age and older.

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating *FENTORA* in elderly patients to provide adequate efficacy while minimizing risk.

ADVERSE REACTIONS
Pre-Marketing Clinical Trial Experience

The safety of *FENTORA* has been evaluated in 304 opioid tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

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The most commonly observed adverse events seen with *FENTORA* are typical of opioid side effects. Opioid side effects should be expected and managed accordingly.

The clinical trials of *FENTORA* were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received *FENTORA* for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of *FENTORA* therapy or cancer-related symptoms.

Table 4 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 4.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100mcg (N= 45)	200mcg (N= 34	400mcg (N= 53)	600mcg (N= 56)	800mcg (N= 113)	Total (N= 304)*
Gastrointestinal disorders						
Nausea	4(9)	5(15)	10(19)	13(23)	18(16)	50(17)
Vomiting	0	2(6)	2(4)	7(13)	3(3)	14(5)
General disorders and administration site conditions						
Fatigue	3(7)	1(3)	9(17)	1(2)	5(4)	19(6)
Nervous system disorders						
Dizziness	5(11)	2(6)	12(23)	18(32)	21(19)	58(19)
Somnolence	2(4)	2(6)	6(12)	7(13)	3(3)	20(7)
Headache	1(2)	3(9)	4(8)	8(14)	10(9)	26(9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 5 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 5.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

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System Organ ClassMeDRA preferred term,n (%)	100mcg(N= 19)	200mcg(N= 31)	400mcg(N= 44)	600mcg(N= 48)	800mcg(N=58)	Total(N= 200)
Blood and lymphatic system disorders						
Anemia	6(32)	4(13)	4(9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4(8)	4 (7)	11(6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13(27)	17(31)	57(29)
Vomiting	7(37)	5(16)	9(20)	8(17)	11(20)	40(20)
Constipation	5(26)	4(13)	5(11)	4(8)	6(11)	24(12)
Diarrhea	3(16)	0	4(9)	3(6)	5(9)	15(8)
Abdominal pain	2(11)	1(3)	4(9)	7(15)	4(7)	18(9)
General disorders and administration site conditions						
Edema peripheral	6(32)	5(16)	4(9)	5(10)	3(5)	23(12)
Asthenia	3(16)	5(16)	2(5)	3(6)	8(15)	21(11)
Fatigue	3(16)	3(10)	9(20)	9(19)	8(15)	32(16)
Infections and infestations						
Pneumonia	1(5)	5(16)	1(2)	1(2)	4(7)	12(6)
Investigations						
Weight decreased	1(5)	1(3)	3(7)	2(4)	6(11)	13(7)
Metabolism and nutrition disorders						
Dehydration	4(21)	0	4(9)	6(13)	7(13)	21(11)
Anorexia	1(5)	2(6)	4(9)	3(6)	6(11)	16(8)
Hypokalemia	0	2(6)	0	1(2)	8(15)	11(6)
Musculoskeletal and connective tissue disorders						
Back pain	2(11)	0	2(5)	3(6)	2(4)	9(5)
Arthralgia	0	1(3)	3(7)	4(8)	3(5)	11(6)
Neoplasms benign, malignant and unspecified incl cysts and polyps)						
Cancer pain	3(16)	1(3)	3(7)	2(4)	1(2)	10(5)
Nervous system disorders						
Dizziness	5(26)	3(10)	5(11)	6(13)	6(11)	25(13)
Headache	2(11)	1(3)	4(9)	5(10)	8(15)	20(10)
Somnolence	0	1(3)	4(9)	4(8)	8(15)	17(9)
Psychiatric disorders						
Confusional state	3(16)	1(3)	2(5)	3(6)	5(9)	14(7)
Depression	2(11)	1(3)	4(9)	3(6)	5(9)	15(8)

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Insomnia	2(11)	1(3)	3(7)	2(4)	4(7)	12(6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1(5)	1(3)	2(5)	4(8)	5(9)	13(7)
Dyspnea	1(5)	6(19)	0	7(15)	4(7)	18(9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of *FENTORA* enrolled. There was no evidence of excess toxicity in this subset of patients.

The duration of exposure to *FENTORA* varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving *FENTORA*. Events are classified by system organ class.

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Anemia, Neutropenia, Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Nausea, Vomiting, Constipation, Abdominal Pain, Diarrhea, Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, , Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Fatigue, Edema Peripheral, Asthenia, Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Pneumonia, Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Weight, Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Dehydration, Anorexia, Hypokalemia, Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Arthralgia, Back Pain, Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Dizziness, Headache, Somnolence, Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy

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Psychiatric Disorders: Confusional State, Depression, Insomnia, Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, Cough, Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

OVERDOSAGE

Clinical Presentation

The manifestations of *FENTORA* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

Immediate management of opioid overdose includes removal of the *FENTORA* tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as ventilatory and circulatory status.

Treatment of Overdosage in the Opioid Non-Tolerant Person

Ventilatory support should be provided, intravenous access obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

Treatment of Overdose in Opioid-Tolerant Patients

Ventilatory support should be provided and intravenous access obtained as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

General Considerations for Overdose

Management of severe *FENTORA* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of *FENTORA*, this is possible with fentanyl and other opioids. If it occurs, it should be

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managed by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

DOSAGE AND ADMINISTRATION
Physicians should individualize treatment using a progressive plan of pain management. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING** and **Dose Titration**).

Patients with hepatic and/or renal impairment
Caution should be exercised for patients with hepatic and/or renal impairment, and the lowest possible dose should be used in these patients. (See **PRECAUTIONS**.)

Patients receiving CYP3A4 inhibitors
Particular caution should be exercised for patients receiving CYP3A4 inhibitors, and the lowest possible dose should be used in these patients (See **PRECAUTIONS**.)

Patients with mucositis
No dose adjustment appears necessary in patients with Grade 1 mucositis. The safety and efficacy of *FENTORA* when used in patients with mucositis more severe than Grade 1 have not been studied.

Administration of *FENTORA*

Dose Titration
Patients should be titrated to a dose of *FENTORA* that provides adequate analgesia with tolerable side effects.

Starting Dose:
The initial dose of *FENTORA* should be 100 mcg.

For patients switching from oral transmucosal fentanyl citrate to *FENTORA*, the starting dose of *FENTORA* should be initiated as shown in Table 6 below (see **PHARMACOKINETICS, Absorption**).

Table 6: Dosing Conversion Recommendations

Current Actiq() Dose (mcg)	Initial *FENTORA* Dose (mcg)
200	100
400	100
600	200
800	200
1200	400

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1600	400

Re-dosing Patients Within a Single Episode: Dosing may be repeated once during a single episode of breakthrough pain if pain is not adequately relieved by one *FENTORA* dose. Re-dosing may occur 30 minutes after the start of administration of *FENTORA* and the same dosage strength should be used.

Increasing the Dose: From an initial dose, patients should be closely followed and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects using a single *FENTORA* tablet. Patients should record their use of *FENTORA* over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted.

Titration should be initiated using multiples of the 100-mcg *FENTORA* tablet. Patients needing to titrate above 100 mcg can be instructed to use two 100-mcg tablets (one on each side of the mouth in the buccal cavity). If this dose is not successful in controlling the breakthrough pain episode, the patient may be instructed to place two 100-mcg tablets on each side of the mouth in the buccal cavity (total of four 100-mcg tablets). Although not bioequivalent, four 100-mcg *FENTORA* tablets were found to deliver approximately 12% and 13% higher values for C_{max} and $AUC_{0-\infty}$, respectively, compared to one 400-mcg *FENTORA* tablet. Consequently, patients converting from four 100-mcg tablets to one 400-mcg *FENTORA* tablet would be expected to experience a decrease in plasma concentration. The impact of this decrease on pain relief has not been evaluated clinically. Titrate above 400 mcg by 200-mcg increments bearing in mind (1) using more than 4 tablets simultaneously has not been studied and (2) it is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

To reduce the risk of overdose during titration, patients should have only one strength *FENTORA* tablet available at any one time. Patients should be strongly encouraged to use all of their *FENTORA* tablets of one strength prior to being prescribed the next strength. If this is not practical, unused *FENTORA* should be disposed of safely (see Disposal of *FENTORA*).

Once a successful dose has been established, if the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated.

Dosage Adjustment

Dosage adjustment of both *FENTORA* and the maintenance (around-the-clock) opioid analgesic may be required in some patients in order to continue to provide adequate relief of breakthrough pain. Generally, the *FENTORA* dose should be increased when patients require more than one dose per breakthrough pain episode for several consecutive episodes.

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Opening the Blister Package
Patients should be instructed not to open the blister until ready to administer. A single blister unit should be separated from the blister card by tearing it apart at the perforations. The blister unit should then be bent along the line where indicated. The blister backing should then be peeled back to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.** The tablet should not be stored once it has been removed from the blister package as the tablet integrity may be compromised and because this increases the risk of accidental exposure to the tablet.

Tablet Administration
Patients should remove the tablet from the blister unit and **immediately** place the entire *FENTORA* tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). **Patients should not attempt to split the tablet**.

The *FENTORA* tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

The *FENTORA* tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the *FENTORA* tablet remain, they may be swallowed with a glass of water.

Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

SAFETY AND HANDLING
FENTORA is supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in *FENTORA* can be fatal to a child. **Patients and their caregivers must be instructed to keep *FENTORA* out of the reach of children** (see **BOX WARNING**, **WARNINGS**, **PRECAUTIONS**, and **MEDICATION GUIDE**).

Store at 20-25ºC (68-77ºF) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

FENTORA should be protected from freezing and moisture. Do not use if the blister package has been tampered with.

DISPOSAL OF FENTORA

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the Medication Guide. If additional assistance is required, referral to the *FENTORA* 800# (1-800-896-5855) should be made.

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HOW SUPPLIED

Each carton contains 7 blister cards with 4 tablets in each card. The blisters are child resistant, encased in peelable foil, and provide protection from moisture. Each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. The dosage strength of each tablet is marked on the tablet, the blister package and the carton. See blister package and carton for product information.

Dosage Strength (fentanyl base)	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 63459-541-28
200 mcg	2	Orange	NDC 63459-542-28
400 mcg	4	Sage green	NDC 63459-544-28
600 mcg	6	Magenta (pink)	NDC 63459-546-28
800 mcg	8	Yellow	NDC 63459-548-28

Note: Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Rx only.

DEA order form required. A Schedule CII narcotic.

Manufactured for:
Cephalon, Inc.
Frazer, PA 19355

By:
CIMA LABS, INC.®
10000 Valley View Road
Eden Prairie, MN 55344

and
Cephalon, Inc
4745 Wiley Post Way
Salt Lake City, UT 84116

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1.1.1.1.1 Label code XXX Date

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Medication Guide

FENTORA™ (fĕn-tor-ă) CII

Cephalon

(fentanyl buccal tablet)
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT: Keep *FENTORA* in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes *FENTORA*, get emergency help right away.

074000106.01

Read the Medication Guide that comes with *FENTORA* before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Share this important information with members of your household.

What is the most important information I should know about *FENTORA*?

1. ***FENTORA* can cause life threatening breathing problems which can lead to death:**
   - **if it is used by anyone who is not already taking other opioid pain medicines and their body is not used to these medicines (not opioid tolerant)**
   - **if it is not used exactly as prescribed**
2. **Your doctor will prescribe a starting dose of FENTORA that is different than other fentanyl containing medicines you may have been taking. Do not substitute FENTORA for other fentanyl medicines, including Actiq, without talking with your doctor.**

What is *FENTORA*?

- *FENTORA* is a prescription medicine that contains the medicine fentanyl. ***FENTORA* is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.**
- ***FENTORA* is used to treat breakthrough pain in adult patients with cancer (18 years of age and older) who are already taking other opioid pain medicines for their constant (around-the-clock) cancer pain.** *FENTORA* is started only after you have been taking other opioid pain medicines and your body has gotten used to them (you are opioid tolerant). **Do not use *FENTORA* if you are not opioid tolerant.**
- You must stay under your doctor's care while taking *FENTORA*.
- ***FENTORA* must not be used for short-term pain from injuries and surgery.**
- **FENTORA should be placed in the mouth, against your gum and allowed to dissolve.** You may feel a gentle bubbling sensation between your cheek and gum as the tablet dissolves. *FENTORA* is not meant to be chewed or swallowed.
- **Prevent theft and misuse. Keep *FENTORA* in a safe place** to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs. **Never give *FENTORA* to anyone else,** even if they have the same symptoms you have. It may harm them and even cause death. **Selling or giving away this medicine is against the law.**

Who should not take *FENTORA*?

Do Not Take *FENTORA* if you:

- are not already taking other opioid pain medicines for your constant (around-the-clock) cancer pain. **Never use *FENTORA* for short-term pain from injuries and surgery.**
- **are allergic to anything in *FENTORA*.** The active ingredient is fentanyl. See the end of this Medication Guide for a complete list of ingredients in *FENTORA*.

What should I tell my doctor before starting *FENTORA*?

Tell your doctor about all of your medical and mental problems, especially the ones listed below:

- Trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- A head injury or brain problem
- Liver or kidney problems
- Seizures (convulsions or fits)
- Slow heart rate or other heart problems
- Low blood pressure
- Mental problems including major depression or hallucinations (seeing or hearing things that are not there)
- A past or present drinking problem or alcoholism, or a family history of this problem
- A past or present drug abuse or addiction problem, or a family history of this problem

Tell your doctor if you are:

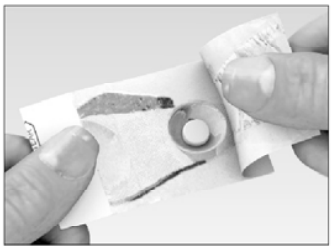
- **pregnant or planning to become pregnant.** *FENTORA* may harm your unborn baby.
- **breast feeding.** *FENTORA* passes through your breast milk, and it can cause serious harm to your baby.

  You should not use *FENTORA* while breast feeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with *FENTORA*. Sometimes, the doses of certain medicines and *FENTORA* need to be changed if used together. **Do not take any medicine while using *FENTORA* until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using *FENTORA*. Be especially careful about taking other medicines that make you sleepy such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.**
Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

How should I use *FENTORA*?

- **Use *FENTORA* exactly as prescribed.** Do not take *FENTORA* more often than prescribed. **Talk to your doctor about your pain. Your doctor can decide if your dose of *FENTORA* needs to be changed.**
- *FENTORA* comes packaged in a blister card. **Do not open the blister until ready to use.** Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. Peel back foil on blister pack to expose tablet.



- **DO NOT push the tablet through the foil** on the blister pack because this could damage the tablet.
- **Once removed from the blister pack, *FENTORA* must be used right away.**

Cephalon	
Cephalon Job No.:	
Draft No.:	1
COLORS: Black	TEXT SIZE: The smallest text on this artwork is at: 10 pt
Product Name	FENTORA
Market	USA
Component	Medication Guide
No. of Colors	1
Dimensions	13-5/32" x 27-1/4"
Barcode	128 based on Item#
Item No.	074000106.01
Date	07/14/06

TINT VALUES
Black and grayscale images

Bar prints 100mm @ 100%

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

- **Place a *FENTORA* tablet in your mouth above a rear molar tooth between the upper cheek and gum and leave in place until the tablet is dissolved. This generally takes between 14 to 25 minutes. After 30 minutes if there is any tablet left, swallow it with a glass of water.** If you cannot take the medicine in this manner, tell your doctor who will advise you what to do. Do not split the tablet.

- **Do not bite, chew or suck *FENTORA* tablets.** If you do so, you will swallow more of the medicine and get less relief for your breakthrough cancer pain.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.

If you have more than 4 episodes of breakthrough cancer pain per day, talk to your doctor. The dose of *FENTORA* may need to be adjusted.

- **If you take too much *FENTORA* or overdose, call 911 for emergency help.**

What should I avoid while taking *FENTORA*?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how *FENTORA* affects how alert you are. *FENTORA* can make you sleepy. Ask your doctor when it is okay to do these activities.
- **Do not drink alcohol while using *FENTORA*.** It can increase your chance of getting dangerous side effects.
- **Do not take any medicine while using *FENTORA* until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using *FENTORA*. Be especially careful about taking other medicines that make you sleepy such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.**

What are the possible or reasonably likely side effects of *FENTORA*?

- ***FENTORA* can cause serious breathing problems that can become life-threatening, especially if used the wrong way.** See "What is the most important information I should know about *FENTORA*?"

Call your doctor or get emergency medical help right away if you:

- **have trouble breathing**
- **have extreme drowsiness with slowed breathing**
- **have slow, shallow breathing (little chest movement with breathing)**
- **feel faint, very dizzy, confused, or have unusual symptoms**

These can be symptoms that you have taken too much (overdose) *FENTORA* or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- ***FENTORA* can cause pain or sores at the application site (on your gum or the inside your cheek).** Tell your doctor if this is a problem for you.
- ***FENTORA* can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.
- ***FENTORA* can cause physical dependence.** Do not stop taking *FENTORA* or any other opioid without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction.
- **There is a chance of abuse or addiction with *FENTORA*.** The chance is higher if you are or have been addicted to or abused other medications, street drugs, or alcohol, or if you have a history of mental problems.

The most common side effects of *FENTORA* are nausea, vomiting, dizziness, sleepiness, headache, and constipation. Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including *FENTORA* and is unlikely to go away without treatment. Talk to your doctor about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking *FENTORA*.

Talk to your doctor about any side effects that bother you or that do not go away.

These are not all the possible side effects of *FENTORA*. For a complete list, ask your doctor.

How should I store *FENTORA*?

- **Keep *FENTORA* in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes *FENTORA*, get emergency help right away.**
- ***FENTORA* is supplied in single sealed child-resistant blister packages.**
- Store *FENTORA* at room temperature, 59° to 86°F (15° to 30°C) until ready to use.
- **Always keep *FENTORA* in a secure place to protect from theft.**

How should I dispose of unopened *FENTORA* tablets when they are no longer needed?

- Dispose of any unopened *FENTORA* tablets remaining from a prescription as soon as they are no longer needed.
- **To dispose of unused *FENTORA*, remove *FENTORA* tablets from blister packages and flush down the toilet. Do not flush the *FENTORA* blister packages or cartons down the toilet.**
- If you need help with disposal of *FENTORA*, call Cephalon at 1-800-896-5855.

General Information About the Safe and Effective Use of *FENTORA*

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use *FENTORA* only for the purpose for which it was prescribed. Do not give *FENTORA* to other people, even if they have the same symptoms you have. ***FENTORA* can harm other people and even cause death. Sharing *FENTORA* is against the law.**

This Medication Guide summarizes the most important information about *FENTORA*. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about *FENTORA* that is written for healthcare professionals. You can also call Cephalon, Inc. at 1-800-896-5855.

What are the ingredients of *FENTORA*?

Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Rx Only.

Cephalon, Inc.
FRAZER, PA 19355, USA

Reference Number 074000106.01
June 23, 2006

U. S. Patent Nos. 6,200,604 and 6,974,590
Printed in USA
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Cephalon

Cephalon Job No.:	
Draft No.:	1
COLORS	TEXT SIZE The smallest text on this artwork is at:
Black	10 pt

Product Name	FENTORA
Market	USA
Component	Medication Guide
No. of Colors	1
Dimensions	13-5/32" x 27-1/4"
Barcode	128 based on Item#
Item No.	074000106.01
Date	07/14/06

TINT VALUES
Black and grayscale images

Bar prints 100mm @ 100%

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FENTORA Carton mockup - 06/27/2006

Place pharmacy label here.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

28 Buccal Tablets

NDC 63459-541-28
Rx only

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **100 mcg** fentanyl base

FOR BUCCAL ADMINISTRATION. DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

WARNING: Keep out of the reach of children.

Read enclosed FENTORA Medication Guide for important warnings and directions.

Cephalon

NDC 63459-541-28
Rx only
28 Buccal Tablets

FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 100 mcg fentanyl base

Each tablet contains fentanyl citrate equivalent to 100 mcg fentanyl base.
Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

LOT
EXP

FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 100 mcg fentanyl base

For buccal administration.
See insert for dosage and administration.

NDC 63459-541-28
Rx only
28 Buccal tablets

For information about this product call: 1-800-896-5855
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Cephalon
Cephalon, Inc.
Frazer, PA 19355

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 100 mcg fentanyl base
FOR BUCCAL ADMINISTRATION.
DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.
WARNING: Keep out of the reach of children.
FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA.

NDC 63459-541-28
Rx only

To the Pharmacist:
Before dispensing:
- ☐ Make sure the patient is opioid tolerant
- ☐ Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
- ☐ Counsel the patient about the use of this product
- ☐ Encourage the patient to read the FENTORA Medication Guide

63459541128

Cephalon	
Cephalon Job No.:	
Draft No.:	1

COLORS

PMS 659 CVC | PMS 109 CVC | Black

Product Name	TRADENAME
Market	USA
Component	28 count 100 mcg
No. of Colors	3
Dimensions	2.876" x 2.206" x 4.53"
Barcode	128 based on NDC#
Item No.	073000146
Date	6/27/06

TINT VALUES

Pantone 659
Gradiant 100% to white

Profile Key
All Over Varnish Unless Marked.
Varnish Free Area

TEXT SIZE
The smallest text on this artwork is at:
7 pt

Bar prints 100mm @ 100%

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FENTORA Carton mockup - 06/27/2006

Place pharmacy label here.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

28 Buccal Tablets

NDC 63459-542-28
Rx only

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **200 mcg** fentanyl base

FOR BUCCAL ADMINISTRATION. DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

WARNING: Keep out of the reach of children.

Read enclosed FENTORA Medication Guide for important warnings and directions.

Cephalon

NDC 63459-542-28
Rx only
28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 200 mcg fentanyl base

Each tablet contains fentanyl citrate equivalent to 200 mcg fentanyl base.
Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

LOT
EXP

NDC 63459-542-28
Rx only
28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 200 mcg fentanyl base

For buccal administration.
See insert for dosage and administration.

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 200 mcg fentanyl base
FOR BUCCAL ADMINISTRATION.
DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.
WARNING: Keep out of the reach of children.
FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA.

NDC 63459-542-28
Rx only

To the Pharmacist:
Before dispensing:
- Make sure the patient is opioid tolerant
- Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
- Counsel the patient about the use of this product
- Encourage the patient to read the FENTORA Medication Guide

634595442 8

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 200 mcg fentanyl base
For information about this product call: 1-800-896-5855
U.S. Patent No. 6,200,604 and 6,974,590
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NDC 63459-542-28
Rx only

Cephalon
Cephalon, Inc.
Frazer, PA 19355

Cephalon	
Cephalon Job No.:	
Draft No.:	1

COLORS

PMS 150 CVC | PMS 109 CVC | Black

Product Name	TRADENAME
Market	USA
Component	28 count 200 mcg
No. of Colors	3
Dimensions	2.876" x 2.206" x 4.53"
Barcode	128 based on NDC#
Item No.	073000147
Date	6/27/06

TINT VALUES

Pantone 150
Gradiant 100% to white

Profile Key
All Over Varnish Unless Marked.
Varnish Free Area

TEXT SIZE
The smallest text on this artwork is at:
7 pt

Bar prints 100mm @ 100%

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FENTORA Carton mockup - 06/27/2006

Place pharmacy label here.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

28 Buccal Tablets

NDC 63459-544-28
Rx only

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **400 mcg** fentanyl base

FOR BUCCAL ADMINISTRATION. DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

⚠ WARNING: Keep out of the reach of children.

Read enclosed FENTORA Medication Guide for important warnings and directions.

Cephalon

NDC 63459-544-28
Rx only
28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 400 mcg fentanyl base

Each tablet contains fentanyl citrate equivalent to 400 mcg fentanyl base.
Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

LOT
EXP

FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 400 mcg fentanyl base

NDC 63459-544-28
Rx only
28 Buccal Tablets

For buccal administration.
See insert for dosage and administration.

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 400 mcg fentanyl base

FOR BUCCAL ADMINISTRATION.
DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

⚠ WARNING: Keep out of the reach of children.

FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA.

NDC 63459-544-28
Rx only

To the Pharmacist:
Before dispensing:
- ☐ Make sure the patient is opioid tolerant
- ☐ Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
- ☐ Counsel the patient about the use of this product
- ☐ Encourage the patient to read the FENTORA Medication Guide

634595544 28

28 Buccal Tablets
NDC 63459-544-28
Rx only

For information about this product call: 1-800-896-5855
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Cephalon
Cephalon, Inc.
Frazer, PA 19355

Cephalon	
Cephalon Job No.:	
Draft No.:	1

COLORS

PMS 577 CVC | PMS 109 CVC | Black

Product Name	TRADENAME
Market	USA
Component	28 count 400 mcg
No. of Colors	3
Dimensions	2.876" x 2.206" x 4.53"
Barcode	128 based on NDC#
Item No.	073000148
Date	6/27/06

TINT VALUES

Pantone 577
Gradiant 100% to white

Profile Key
All Over Varnish Unless Marked.
Varnish Free Area

TEXT SIZE
The smallest text on this artwork is at:
7 pt

Bar prints 100mm @ 100%

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FENTORA Carton mockup - 06/27/2006

Place pharmacy label here.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

28 Buccal Tablets

NDC 63459-546-28
Rx only

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **600 mcg** fentanyl base

FOR BUCCAL ADMINISTRATION. DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

⚠ WARNING: Keep out of the reach of children.

Read enclosed FENTORA Medication Guide for important warnings and directions.

Cephalon

NDC 63459-546-28
Rx only
28 Buccal Tablets

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **600 mcg** fentanyl base

Each tablet contains fentanyl citrate equivalent to 600 mcg fentanyl base.
Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

LOT
EXP

FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to **600 mcg** fentanyl base

For buccal administration.
See insert for dosage and administration.

NDC 63459-546-28
Rx only
28 Buccal tablets

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to **600 mcg** fentanyl base

For information about this product call: 1-800-896-5855
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Cephalon, Inc.
Frazer, PA 19355

FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to **600 mcg** fentanyl base
FOR BUCCAL ADMINISTRATION.
DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids
such as fentanyl or morphine.
⚠ WARNING: Keep out of the reach of children.

FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA.

To the Pharmacist:
Before dispensing:
- ☐ Make sure the patient is opioid tolerant
- ☐ Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
- ☐ Counsel the patient about the use of this product
- ☐ Encourage the patient to read the FENTORA Medication Guide

NDC 63459-546-28
Rx only
28 Buccal Tablets

6345954628

Cephalon	
Cephalon Job No.:	
Draft No.:	1

COLORS

PMS 243 CVC | PMS 109 CVC | Black

Product Name	TRADENAME
Market	USA
Component	28 count 600 mcg
No. of Colors	3
Dimensions	2.876" x 2.206" x 4.53"
Barcode	128 based on NDC#
Item No.	073000149
Date	6/27/06

TINT VALUES

Pantone 243
Gradiant 100% to white

Profile Key
All Over Varnish Unless Marked.
Varnish Free Area

TEXT SIZE
The smallest text on this artwork is at:
7 pt

Bar prints 100mm @ 100%

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For current labeling information, please visit https://www.fda.gov/drugsatfda

FENTORA Carton mockup - 06/27/2006

Place pharmacy label here.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

28 Buccal Tablets

NDC 63459-548-28
Rx only

FENTORA™ Ⓒ
(fentanyl buccal tablet)

equivalent to **800 mcg** fentanyl base

FOR BUCCAL ADMINISTRATION. DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.

⚠ WARNING: Keep out of the reach of children.

Read enclosed FENTORA Medication Guide for important warnings and directions.

Cephalon

NDC 63459-548-28
Rx only
28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 800 mcg fentanyl base

Each tablet contains fentanyl citrate equivalent to 800 mcg fentanyl base.
Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

LOT
EXP

For buccal administration.
See insert for dosage and administration.

For information about this product call: 1-800-896-5855
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Cephalon
Cephalon, Inc.
Frazer, PA 19355

28 Buccal Tablets
FENTORA™ Ⓒ
(fentanyl buccal tablet)
equivalent to 800 mcg fentanyl base
FOR BUCCAL ADMINISTRATION.
DO NOT SWALLOW TABLET WHOLE.
Only for patients already taking opioids such as fentanyl or morphine.
⚠ WARNING: Keep out of the reach of children.
FENTORA contains medicine that could be harmful or fatal to someone who has not been prescribed FENTORA.
NDC 63459-548-28
Rx only

To the Pharmacist:
Before dispensing:
- ☐ Make sure the patient is opioid tolerant
- ☐ Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
- ☐ Counsel the patient about the use of this product
- ☐ Encourage the patient to read the FENTORA Medication Guide

6345954828

Cephalon	
Cephalon Job No.:	
Draft No.:	1

COLORS

PMS 1215 CVC | PMS 109 CVC | Black

Product Name	TRADENAME
Market	USA
Component	28 count 800 mcg
No. of Colors	3
Dimensions	2.876" x 2.206" x 4.53"
Barcode	128 based on NDC#
Item No.	073000150
Date	6/27/06

TINT VALUES

Pantone 1215
Gradiant 100% to white

Profile Key
All Over Varnish Unless Marked.
Varnish Free Area

TEXT SIZE
The smallest text on this artwork is at:
7 pt

Bar prints 100mm @ 100%

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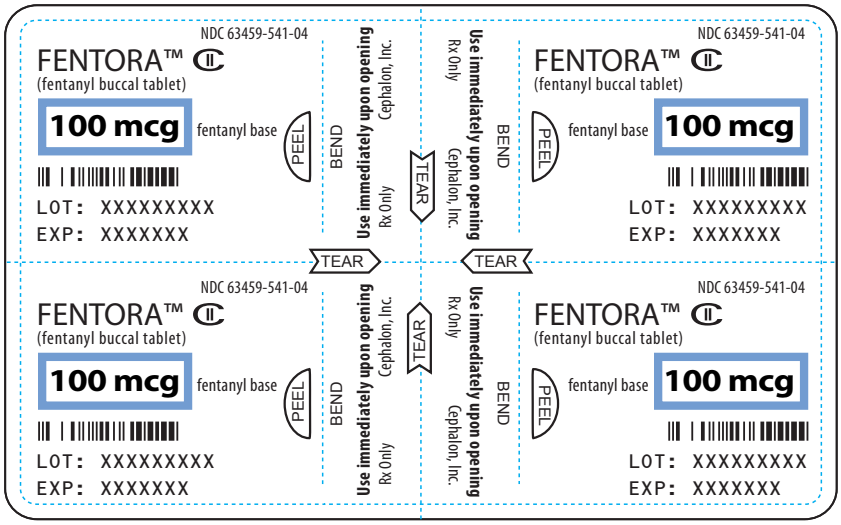
For current labeling information, please visit https://www.fda.gov/drugsatfda

Cephalon

Product Labeling Artwork

FENTORA 100 mcg blister, flat side

June 27, 2006



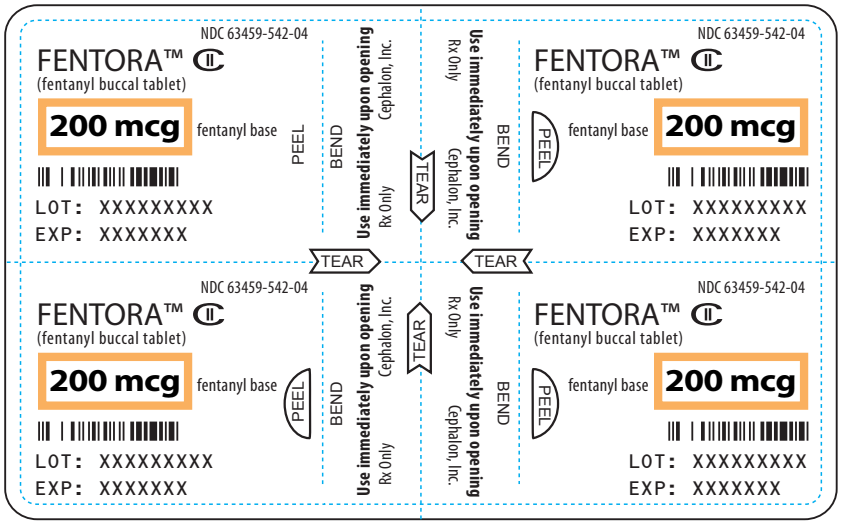
This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Cephalon

Product Labeling Artwork

FENTORA 200 mcg blister, flat side

June 27, 2006



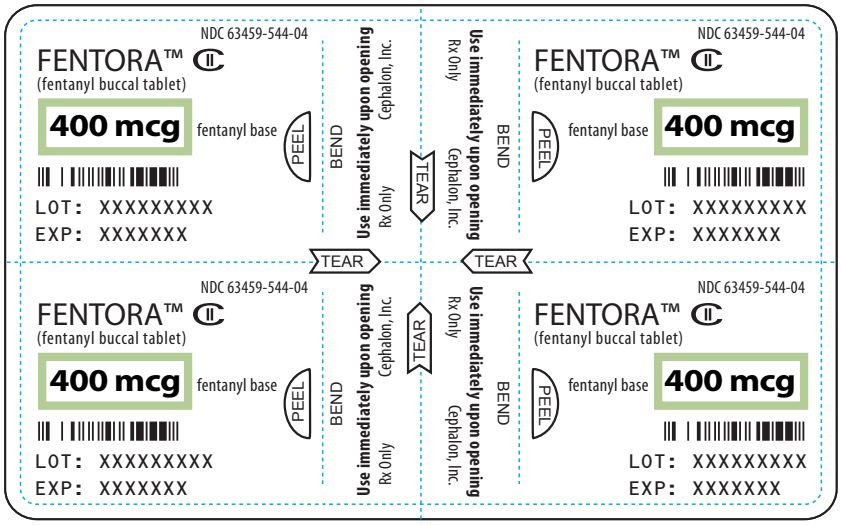
This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Cephalon

Product Labeling Artwork

FENTORA 400 mcg blister, flat side

June 27, 2006



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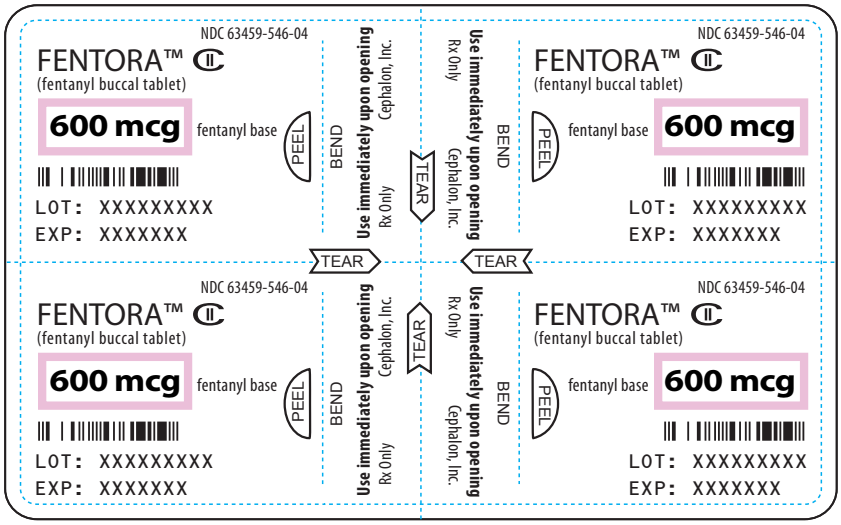
Cephalon

Product Labeling Artwork

FENTORA 600 mcg blister, flat side

June 27 2006



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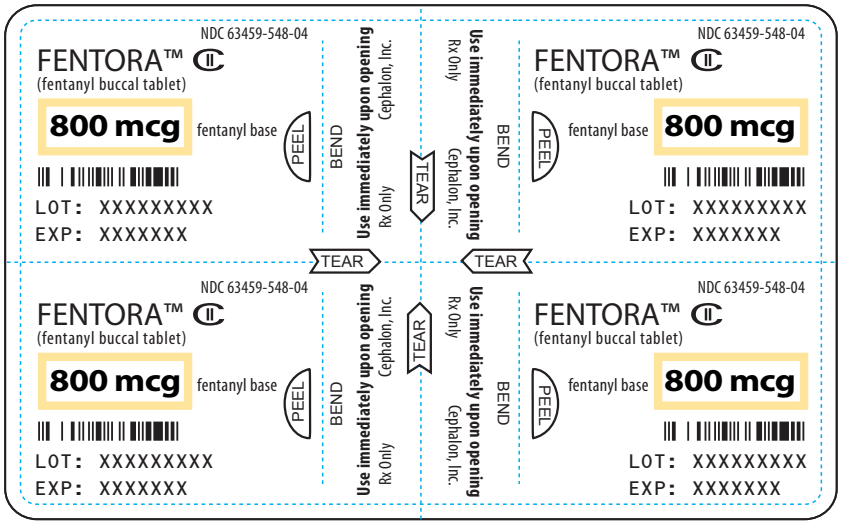
Cephalon

Product Labeling Artwork

FENTORA 800 mcg blister, flat side

June 27, 2006



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FENTORA® RISK MINIMIZATION ACTION PLAN: SUMMARY

The FENTORA® Risk Minimization Action Plan is a program designed to reduce the risk of serious adverse events resulting from use in opioid non-tolerant patients, misuse, and unintended (accidental) exposure. The risks of FENTORA® treatment are addressed through education of prescribers, pharmacists, patients and caregivers, surveillance for events, and assessment of the effectiveness of the FENTORA Risk Minimization Action Plan to determine the need for improvement.

1. Goals for the FENTORA Risk Minimization Action Plan
    - FENTORA should not be used by opioid non-tolerant cancer patients.
    - No misuse of FENTORA should occur.
    - Unintended (accidental) exposure to FENTORA should not occur.

2. Key elements of risk minimization

    Cephalon had developed the Risk Minimization Action Plan around the following four elements to communicate to all stakeholders:

    - Labeling
    - Education Program
    - Surveillance Program
    - Intervention

3. Labeling

    3.1 Package Insert

    The package insert forms the basis for education and communication tool development.

    - A Boxed Warning emphasizes key safety messages
        - FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics.
        - 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.
        - Off label use that can be particularly dangerous because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients.
        - FENTORA is contraindicated in the management of acute or postoperative pain.
        - FENTORA is not indicated for use in opioid non-tolerant patients.
        - Accidental exposure in must be avoided in children. Patients and their caregivers must be instructed that the product 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.
        - Warning that the dose must be adjusted when converting patients from Actiq because of differences in relative bioavailability.

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- Emphasis that FENTORA is only for use in opioid tolerant cancer patients by healthcare professionals knowledgeable and skilled in the use of Schedule II opioids.

- The Clinical Pharmacology section and Dosage and Administration sections stress the greater relative bioavailability of FENTORA compared to ACTIQ and the need to use a conservative conversion ratio for transferring patients from ACTIQ to FENTORA.

3.2 Carton labeling

- A box with a four point checklist for the pharmacist is present on the carton
  - Make sure the patient is opioid tolerant
  - Do not substitute FENTORA for other oral fentanyl products on a mcg per mcg basis
  - Counsel the patient about the use of the product
  - Encourage the patient to read the FENTORA Medication Guide

3.3 A Medication Guide has been approved to provide patients with information required for safe use of FENTORA.

4. Educational Program

Cephalon will provide prescribers, pharmacists, and patients/caregivers with educational materials on the key safety messages of FENTORA in the following formats:

- "Dear Healthcare Provider" style letters to prescribers and pharmacists
- An educational monograph for physicians
- Counseling messages to prescribers and pharmacists with counseling aids
- Detailing visits from trained field representatives
- Publications in pharmaceutical compendia
- Formal presentations (Speakers Bureau and CME)
- A Risk Minimization Action Plan flashcard

5. Surveillance Program

Cephalon will maintain active and passive surveillance methods to detect prescribing patterns not consistent with labeling, signs of misuse, signs of unintentional exposure, particularly accidental exposure in children, and serious adverse events. Existing national databases will be to follow spontaneous reporting of adverse events, prescribing patterns, emergency room mentions of misuse of FENTORA, state medical examiner and poison control evidence of overdose, and state and private surveillance databases for evidence of misuse. Surveys developed by Cephalon will be used to monitor the results of educational efforts for physicians, pharmacists, and patients.

6. Intervention

Cephalon will periodically evaluate the effectiveness of the components of the RiskMAP and make adjustments as appropriate.

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7. Accidental Exposure

Unused drug available in the home is a source of unintentional overdose and misuse by persons for whom FENTORA was not prescribed. To reduce the volume of unused drug in the home, Cephalon has designed a product return and disposal program for patients and pharmacists.