

media fact sheet

FENTORA® (FENTANYL BUCCAL TABLET) [C-II]

What is
FENTORA?

FENTORA® (fentanyl buccal tablet) [C-II] is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

FENTORA (fěn-tor'-ă) is an opioid pain medication containing fentanyl that is manufactured as a sugar-free tablet that is designed to provide rapid absorption of the medication through the buccal (bü -käl) mucosa, the lining of the upper cheek.

What is
breakthrough
pain?

Nearly 50 million Americans suffer from chronic pain, a condition which often consists of two distinct components:

- Persistent pain: pain that is constant throughout the day that is often managed with around-the-clock opioids
- Breakthrough pain: flares of moderate to severe pain commonly characterized by their rapid onset, unpredictability, and relatively short duration which occur in the context of otherwise well-managed persistent pain

Breakthrough pain in patients with cancer needs independent assessment and treatment as part of an integrated chronic pain management plan.

An estimated 51-89 percent of all patients suffering from cancer and controlled persistent pain may also experience breakthrough pain. Breakthrough pain can commonly be characterized by its rapid onset, unpredictability, and relatively short duration. A typical breakthrough pain episode in patients with cancer may peak in as little as three minutes, last 30 minutes, and occur up to four times a day. (These numbers are based on medians, the midpoint of the range of data observed in studies.) Breakthrough pain is often treated with opioids that are taken as needed at the start or in anticipation of an episode.

What does it
mean when a
person is
tolerant to
opioid therapy?

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer. It is important to know that opioid tolerance here does not refer to analgesic tolerance which is a need to increase the dose of a drug to obtain the same amount of pain relief. In addition, patients often confuse opioid tolerance with lack of tolerability such as nausea and vomiting.

How does
FENTORA work?

FENTORA is placed between the upper cheek and gum above a rear molar tooth. When the tablet comes in contact with saliva, FENTORA's proprietary OraVescent® drug delivery system— developed by Cephalon subsidiary CIMA LABS—generates a chemical reaction leading to the release of carbon dioxide.

It is believed that transient pH changes accompanying this reaction may optimize how the tablet dissolves and how the medicine passes through the buccal mucosa. With this technology, approximately 48 percent of the medicine is absorbed directly across the buccal mucosa and into the bloodstream.

As soon as the fentanyl enters the bloodstream, it is carried to the central nervous system—the brain and spinal cord—where it begins to work to relieve pain. The rest of the medicine is swallowed and absorbed more slowly through the stomach and intestines resulting in an absolute bioavailability of approximately 65 percent.

Conventional short-acting oral opioids, often used to treat breakthrough pain, are swallowed and absorbed in the gastrointestinal tract, and can take up to 30-45 minutes to take effect.

How has the effectiveness of *FENTORA* been evaluated?

The New Drug Application (NDA) submission for *FENTORA* included data from 13 clinical studies. The pivotal randomized, double-blind, placebo-controlled study assessed the efficacy and safety of *FENTORA* compared with placebo in adult patients with cancer and breakthrough pain who were already receiving around-the-clock opioid medication for their persistent cancer pain.

In the pivotal study of *FENTORA*, clinically significant decreases in pain intensity and greater pain relief were observed in some patients within 15 minutes, the first time point measured, and maintained through 60 minutes, the last time point measured.

What is important to know about the safety of *FENTORA*?

When prescribing *FENTORA*, it is important to remember:

- *FENTORA* is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
- Only use *FENTORA* in opioid-tolerant patients.
- Life-threatening respiratory depression could occur at any dose in patients not taking chronic opiates.
- Contraindicated in management of acute or postoperative pain, including headache/migraines and dental pain.
- Contains medicine in an amount that can be fatal to a child. Keep out of reach of children.
- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to *FENTORA*.
- When dispensing, do not substitute a *FENTORA* prescription for other fentanyl products.
- Use with CYP 3A4 inhibitors may cause potentially fatal respiratory depression.
- Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics.

Serious adverse events associated with all opioids including *FENTORA* are respiratory depression, circulatory depression, hypotension, and shock. All patients should be followed for symptoms of respiratory depression. Deaths have occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The most common (≥ 10 percent) adverse events observed in all *FENTORA* cancer clinical trials were nausea, vomiting, fatigue, dizziness, anemia, constipation, peripheral edema, dehydration, weakness and headache. Most side effects were mild-to-moderate in severity. In addition, application site reactions which occurred in 10 percent of patients in all *FENTORA* studies ranged from paresthesia to ulceration and bleeding. These adverse events tended to occur early in treatment, were self-limited, and resulted in treatment discontinuation for two percent of patients.

Please also see Important Safety Information including Boxed Warning at the end of this fact sheet.

How long has *FENTORA* been available?

FENTORA was approved by the U.S. Food and Drug Administration (FDA) on September 25, 2006 and was made available in the U.S. in October 2006. An identical formulation, *EFFENTORA*[®] (fentanyl effervescent buccal tablet), was approved in the EU in April 2008.

In what dosage strengths is *FENTORA* available?

FENTORA is packaged in cartons containing 28 tablets (seven child-resistant blister cards with four tablets in each card) and is available in five dosage strengths: 100 / 200 / 400 / 600 / 800 mcg.

Does *FENTORA* have the potential for misuse, abuse, addiction, or overdose?

All opioids have important benefits in alleviating pain, but are associated with a risk of misuse, abuse, addiction, and overdose. *FENTORA* contains an opioid agonist (fentanyl) that is a Schedule II controlled substance with a potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Concerns about misuse, abuse, addiction, and overdose should not prevent the proper management of pain; however, all patients treated with opioids require careful monitoring.

Cephalon markets *FENTORA* under a comprehensive Food and Drug Administration (FDA) approved Risk Evaluation and Mitigation Strategy (REMS) to mitigate potential risks of misuse, abuse, addiction, and overdose. For more information visit www.actiqandfentorarems.com.

Who makes *FENTORA*? *FENTORA* is manufactured by Cephalon, Inc. (Nasdaq: CEPH), Frazer, PA, an international biopharmaceutical company.

Through the CephalonCares FoundationSM, Cephalon works to improve patient access to medication and assure that barriers to receiving treatment due to cost are minimized. The CephalonCares Foundation Patient Assistance Programs provides Cephalon, Inc., medications at no cost to patients in the United States who meet certain insurance and income criteria. For more information about this program, visit www.cephalon.com.

There is a boxed warning for *FENTORA*. Please read the following important safety information:

<p>WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE</p> <p>Reports of serious adverse events, including deaths in patients treated with <i>FENTORA</i> have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. <u>The substitution of <i>FENTORA</i> for any other fentanyl product may result in fatal overdose.</u></p> <p><i>FENTORA</i> is indicated only for the management of breakthrough pain in adult patients with cancer who are <u>already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.</u> Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.</p> <p><i>FENTORA</i> is contraindicated in the management of acute or postoperative pain including headache/migraine. <i>FENTORA</i> is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.</p> <p>Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.</p> <p><u>When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to <i>FENTORA</i>. Carefully consult the Initial Dosing Recommendations table. [See <i>Dosage and Administration</i> (2.1)]</u></p> <p><u>When dispensing, do not substitute a <i>FENTORA</i> prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of <i>FENTORA</i> compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of <i>FENTORA</i> for any other fentanyl product may result in fatal overdose.</u></p> <p>Special care must be used when dosing <i>FENTORA</i>. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See <i>Dosage and Administration</i> (2.1)]</p> <p><i>FENTORA</i> contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. <i>FENTORA</i> can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing <i>FENTORA</i> 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.</p> <p>Patients and their caregivers must be instructed that <i>FENTORA</i> 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 <i>Patient Counseling Information</i> (17.1) and <i>How Supplied/Storage and Handling</i> (16.1)]</p> <p><i>FENTORA</i> 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.</p> <p>The concomitant use of <i>FENTORA</i> with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see <i>Drug Interactions</i> (7)].</p> <p>Because of the risk for misuse, abuse, addiction, and overdose, <i>FENTORA</i> is available only through a restricted distribution program, required by the Food and Drug Administration, called the <i>FENTORA</i> REMS Program (Risk Evaluation and Mitigation Strategy). Under the <i>FENTORA</i> REMS Program, healthcare professional (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute <i>FENTORA</i>, respectively. [See <i>Warnings and Precautions</i> (5.11)] Further information is available at www.actiqandfentorarems.com or by calling 1-888-688-6885.</p>
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Indication: *FENTORA* is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

The following is not a complete list; please see full prescribing information.

Contraindications:

- *FENTORA* must not be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients
- *FENTORA* is contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- *FENTORA* is contraindicated in patients with known intolerance or hypersensitivity to fentanyl, *FENTORA*, any of its components

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate *FENTORA* cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer *FENTORA* with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding
- *FENTORA* is available only through a restricted distribution program called the *FENTORA* REMS Program

Adverse Reactions:

- Most common adverse reactions during titration phase (frequency $\geq 10\%$): nausea and dizziness. Most common additional adverse reactions during longer-term treatment (frequency $\geq 10\%$): vomiting, fatigue, anemia, constipation, peripheral edema, asthenia, dehydration, and headache.

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of inhibitors of CYP 3A4, for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4, for signs of opioid toxicity

Use in Specific Populations:

- Safety and efficacy below age 18 years have not been established.
- Systemic exposure was higher for women than men and was attributed to differences in weight
- Administer *FENTORA* with caution to patients with severe hepatic or renal disease

For more information about *FENTORA*, including the boxed warning, please visit www.FENTORA.com or contact Cephalon Medical Services at 800-896-5855.

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