

media fact sheet

ACTIQ[®] (ORAL TRANSMUCOSAL FENTANYL CITRATE) [C-II]

What is *ACTIQ*?

ACTIQ[®] (oral transmucosal fentanyl citrate) [C-II] is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

ACTIQ is an opioid pain medication containing fentanyl that is manufactured as a medicated single-use lozenge on a handle that is designed to dissolve slowly in the mouth to facilitate absorption of the medication through the oral mucosa, the inner lining of the 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 will 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 oral 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 *ACTIQ* work?

Patients move the *ACTIQ* unit along the inside of their cheeks to facilitate the absorption of fentanyl. Over the 15-minute consumption period, 25 percent of the pain medication rapidly passes through the highly permeable lining of the oral mucosa. 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 relieve pain. The remaining medicine is swallowed and absorbed more slowly through the stomach and intestines, resulting in an additional 25 percent of the total dose to enter the bloodstream for more prolonged duration of analgesia. 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 *ACTIQ* been evaluated? Clinical studies involved 257 opioid-tolerant cancer patients at more than 45 sites in the U.S. In the pivotal study, *ACTIQ* provided significant relief of breakthrough pain in cancer patients compared to placebo. Pain relief may be observed within 15 minutes while consuming an *ACTIQ* unit, but full relief may not be experienced for up to 45 minutes after finishing an *ACTIQ* unit.

What is important to know about the safety of *ACTIQ*? *ACTIQ* is a prescription medicine that contains fentanyl. *ACTIQ* 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. *ACTIQ* is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying cancer pain. *ACTIQ* can cause life-threatening breathing problems which can lead to death in patients who are not regularly using other opioid pain medicines around-the-clock for their constant cancer pain and whose body is not used to these medicines. *ACTIQ* must not be used for the treatment of short-term pain from injuries, surgery, dental pain and headaches, including migraines. Deaths have occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. In addition, deaths have been reported in children who have accidentally taken *ACTIQ*. *ACTIQ* should not be substituted for other fentanyl medicines, including *FENTORA*[®] (fentanyl buccal tablet CII), without talking with a doctor. The substitution for any other fentanyl product may result in fatal overdose.

The most serious adverse effects associated with all opioids including *ACTIQ* are respiratory depression (potentially leading to apnea and respiratory arrest), circulatory depression, hypotension, and shock. All patients should be followed for symptoms of respiratory depression. The most common adverse reactions observed with *ACTIQ* during titration phase (frequency $\geq 5\%$) were: nausea, dizziness, somnolence, vomiting, asthenia, and headache. Frequently, however, some of these adverse events will cease or decrease in intensity with continued use of *ACTIQ*, as the patient is titrated to the proper dose. The most common additional adverse reactions during longer-term treatment (frequency $\geq 5\%$) were dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. Postmarketing reports of dental decay of varying severity including dental caries, tooth loss, and gum line erosion have been received in patients taking *ACTIQ*.

ACTIQ should be kept in a safe place to prevent theft and misuse and should not be given to anyone else.

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

Does *ACTIQ* have the potential for misuse, abuse, addiction, or overdose? All opioids, including *ACTIQ*, have important benefits in alleviating pain, but are associated with a risk of misuse, abuse, addiction, and overdose. *ACTIQ* contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Concerns about misuse, abuse, addiction, and overdose should not prevent the proper management of pain; however, all patients treated with *ACTIQ* should be carefully monitored.

Cephalon markets *ACTIQ* under a comprehensive Food and Drug Administration (FDA) approved Risk Evaluation and Mitigation (REMS) program. For more information visit www.actiqandfentorarems.com.

ACTIQ contains a medicine in an amount that can be fatal to children. Patients and caregivers are advised to keep units out of the reach of children and dispose of open units properly. To minimize risks to children and to ensure the safe storage and disposal of *ACTIQ* units, all patients are encouraged to obtain a free Child Safety Kit. The kit includes a fanny pack with a lock, a child-resistant storage container, important safety information, as well as educational materials for patients, caregivers, and children.

In what dosage strengths is *ACTIQ* available? *ACTIQ* is available in six dosage strengths: 200 / 400 / 600 / 800 / 1200/ 1600 microgram (mcg). The recommended starting dose of *ACTIQ* is 200 mcg.

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

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

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. 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 of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ 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 ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take **ONLY ONE** additional dose using the same strength and then must wait at least 4 hours before taking another dose [see *Dosage and Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ 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.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see *Warnings and Precautions (5.3)*, *Patient Counseling Information (17.5, 17.6)*, and *How Supplied/Storage and Handling (16.2)*].

ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted distribution program, required by the Food and Drug Administration, called the ACTIQ REMS Program (Risk Evaluation and Mitigation Strategy). Under the ACTIQ REMS Program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [See *Warnings and Precautions (5.10)*] Further information is available at www.actiqandfentorarems.com or by calling 1-888-688-6885.

Indication: ACTIQ is an opioid analgesic indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients must remain on around-the-clock opioids when taking ACTIQ.

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

Contraindications:

- ACTIQ 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
- ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("ACTIQ Child Safety Kit")
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ with extreme caution in patients susceptible to intracranial effects of CO₂ retention
- ACTIQ is available only through a restricted distribution program called the ACTIQ REMS Program

Adverse Reactions:

- Most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common additional adverse reactions during longer-term treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.

Postmarketing Experience:

- Postmarketing reports of dental decay of varying severity including dental caries, tooth loss, and gum line erosion have been received in patients taking ACTIQ

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 effectiveness in pediatric patients below 16 years of age have not been established
- Administer ACTIQ with caution to patients with liver or kidney dysfunction

Full prescribing information about *ACTIQ*, including boxed warning, is available at www.actiq.com or from Cephalon Medical Services (1-800-896-5855).

Child Safety Kits can be ordered online, by calling toll free (1-800-896-5855), or from the patient's health care professional or pharmacist.

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