

FENTANYL CITRATE TRANSMUCOSAL UTILIZATION MANAGEMENT CRITERIA

DRUG CLASS:	Fentanyl citrate transmucosal
BRAND (generic) NAMES:	Actiq (fentanyl citrate) lozenge on a handle 200, 400, 600, 800, 1200, 1600 mcg
HICL = H3AT	Fentora (fentanyl citrate) buccal tablet 100, 200, 300, 400, 600, 800 mcg

COVERAGE AUTHORIZATION CRITERIA for fentanyl citrate lozenges (Actiq and generics) and buccal tablets (Fentora):

Indicated for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy.

- 1) Patients have breakthrough pain due to cancer.
- 2) Patients must already be receiving chronic opioid therapy, preferably long-acting dosage forms of opioid therapy.
- 3) Patients considered opioid tolerant are those who are taking, for one week or longer,
 - at least 60 mg morphine/day,
 - at least 25 mcg transdermal fentanyl/hour,
 - at least 30 mg of oxycodone daily,
 - at least 8 mg oral hydromorphone daily, or
 - an equianalgesic dose of another opioid.
- 4) Patients must be 16 years of age or older.
- 5) For patients who are able to take other oral immediate-release narcotics for management of their breakthrough pain: Patients must have tried and failed or not tolerated **at least one** other short-acting, immediate-release opioid therapy for their cancer pain. Other short-acting opioids include
 - Immediate-release morphine (tablet, solution, suppository)
 - Immediate-release oxycodone and combinations (e.g., Roxicodone, OxyFast, OxyIR, Combunox, Percocet, Roxicet, Percodan, generics)
 - Hydromorphone (e.g., Dilaudid, generics)
 - Hydrocodone-containing products (e.g., Vicodin, Lorcet, Lortab, Xodol, Zydone, Norco, Anexsia, Vicoprofen, Reprexain, generics)
- 6) No contraindications such as the following are present:
 - use in the management of acute or postoperative pain (including headache/migraine),
 - patients who are not taking chronic opiates,
 - patients who are not opioid-tolerant,
 - hypoxia or hypercarbia,
 - intolerance or hypersensitivity to fentanyl
- 7) The requested quantity must be 4 units per day or less (120 lozenges or tablets per 30 days or less). For patients who are still in the titration process of determining their effective dose, larger quantities of up to 180 units per 30 days may be approved.

FDA-APPROVED INDICATIONS

Fentanyl citrate lozenges (Actiq):

Fentanyl citrate lozenges (Actiq, generics) are 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 opioid therapy for their underlying persistent cancer pain.

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Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg 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 taking chronic opiates. For this reason, Actiq is contraindicated in the management of acute or postoperative pain.

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.

FDA-APPROVED INDICATIONS

Fentanyl citrate buccal tablets (Fentora):

Fentora is indicated only for the management of breakthrough pain in patients with cancer 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 oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. 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.

BLACK BOX WARNINGS:

Fentanyl citrate lozenges (Actiq)

Fentanyl citrate buccal tablets (Fentora)

IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

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

Fentanyl citrate oral transmucosal 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, for one week or longer in around-the-clock doses:

- at least 60 mg morphine/day,
- at least 25 mcg transdermal fentanyl/hour,
- at least 30 mg of oxycodone daily,
- at least 8 mg oral hydromorphone daily, or
- an equianalgesic dose of another opioid.

Fentanyl citrate oral transmucosal is intended to be used only in the care of cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, fentanyl citrate oral transmucosal is contraindicated in the management of acute or postoperative pain. This product must not be used in opioid non-tolerant patients, including those with only as needed (PRN) prior exposure.

Patients and their caregivers must be instructed that fentanyl citrate lozenges and buccal tablets contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets and



lozenges out of the reach of children, and opened units properly discarded. The concomitant use of fentanyl citrate with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Additional Black Box Warnings for fentanyl citrate buccal tablets (Fentora):

Reports of serious adverse events, including deaths in patients treated with Fentora 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 Fentora for any other fentanyl product may result in fatal overdose.

Fentora is contraindicated in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from Actiq (fentanyl citrate lozenges) to Fentora. Carefully consult approved dosing recommendations. When dispensing, do not substitute a Fentora prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of Fentora 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 Fentora for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing Fentora. 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.

RATIONALE:

These fentanyl citrate oral transmucosal products **must not be used in opioid non-tolerant patients** because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates.

The FDA-approved labeling is very clear that these drugs are to be used **ONLY** for breakthrough pain in patients with cancer.

Inappropriate use of these drugs may cause serious respiratory depression and death.

If clinically appropriate, fentanyl citrate transmucosal products are covered when the use of other less costly narcotics is not an option.

DOSAGE AND ADMINISTRATION

Fentanyl citrate lozenges (Actiq):

- **Initial dosing:** The initial dose of Actiq to treat episodes of breakthrough cancer pain is 200 mcg. Patients should be prescribed an initial titration supply of six 200 mcg Actiq units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.
- From this initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single Actiq dosage unit per breakthrough cancer pain episode.
- If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased.
- Until the appropriate dose is reached, patients may find it necessary to use an additional Actiq unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase, no more than two units should be taken for each individual breakthrough cancer pain episode.
- **Increasing the dose:** If treatment of several consecutive breakthrough cancer pain episodes requires more than one Actiq per episode, consider an increase in dose to the next higher available strength. At each new dose of Actiq during titration, it is recommended that six units of the titration dose be prescribed. Evaluate each new dose of Actiq used in the titration period over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects.
- **Maintenance:** Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. Consider increasing the around-the-clock opioid dose used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.



- **Administration:** The patient should place the Actiq unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The Actiq unit should be sucked, not chewed. A unit dose of Actiq, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.
- The Actiq unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy. If signs of excessive opioid effects appear before the unit is consumed, remove the drug matrix from the patient's mouth immediately and decrease future doses.
- **Discontinuation:** For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

DOSAGE AND ADMINISTRATION

Fentanyl citrate buccal tablets (Fentora):

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose. Patients should be strongly encouraged to use all of their Fentora tablets of one strength prior to being prescribed the next strength.

- **Initial dosing:** For opioid-tolerant patients **not** being converted from Actiq, the initial dose of Fentora is **always** 100 mcg.
- For patients being converted from Actiq, prescribers must use the Dosing Recommendations table in the Fentora product labeling.
- In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of Fentora for any episode of breakthrough pain. Patients **MUST** wait **at least 4 hours** before treating another episode of breakthrough pain with Fentora.
- **Increasing the dose:** From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects.
- Patients whose initial dose is 100 mcg and who need to titrate to a higher dose can be instructed to use two 100-mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, 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). Titrate using multiples of the 200-mcg Fentora tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
- Patients **MUST** wait **at least 4 hours** before treating another episode of breakthrough pain with Fentora. To reduce the risk of overdose during titration, patients should have only one strength of Fentora tablets available at any one time.
- **Maintenance:** Once titrated to an effective dose, patients should generally use **only ONE** Fentora tablet of the appropriate strength per breakthrough pain episode.
- On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Patients **MUST** wait **at least 4 hours** before treating another episode of breakthrough pain with Fentora.
- Dosage adjustment of Fentora may be required in some patients in order to continue to provide adequate relief of breakthrough pain. Generally, the Fentora dose should be increased only when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.
- 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.
- **Patients with hepatic and/or renal impairment or receiving CYP3A4 inhibitors:** Caution should be exercised, and the lowest possible dose should be used in these patients.
- **Tablet Administration:** Once the tablet is removed from the blister unit, the patient should immediately place the entire Fentora tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). **Patients should not 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.
- It is recommended that patients alternate sides of the mouth when administering subsequent doses of Fentora.

DRUG INTERACTIONS:

- **CYP3A4 inhibitors:** The concomitant use of transmucosal fentanyl citrate with strong CYP3A4 inhibitors (e.g, ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving fentanyl citrate concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.
- **Grapefruit:** Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, and thus should be avoided.
- **CYP3A4 inducers:** Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.
- **MAO inhibitors:** Concomitant use of fentanyl citrate with an MAO inhibitor, or within 14 days of discontinuation, is not recommended.

ADDITIONAL DRUG INFORMATION:

- Cephalon Medical Services
Phone: 1-800-896-5855

References:

Actiq (fentanyl citrate). Product Information. Cephalon. 2007.

Fentora (fentanyl citrate). Product Information. Cephalon. 2007.

