

6) The requested quantity must be 4 units per day or less (120 units per 30 days or less). For patients who are still in the titration process of determining their effective dose, larger quantities (e.g., 180 units per 30 days) may be approved.

FDA-APPROVED INDICATIONS

Fentanyl citrate lozenges (Actiq)

Fentanyl citrate buccal tablets (Fentora)

Fentanyl buccal soluble film (Onsolis)

Fentanyl sublingual tablets (Abstral)

Fentanyl nasal spray (Lazanda)

Fentanyl lozenges (Actiq, generics), buccal tablets (Fentora), buccal soluble film (Onsolis), sublingual tablets (Abstral) and nasal spray (Lazanda) are indicated only for the management of breakthrough cancer pain in patients **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 oral morphine/day, at least 25 mcg 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.

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, transmucosal fentanyl is contraindicated in the management of acute or postoperative pain. Transmucosal fentanyl 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.

BLACK BOX WARNINGS

Fentanyl citrate lozenges (Actiq)

Fentanyl citrate buccal tablets (Fentora)

Fentanyl buccal soluble film (Onsolis)

Fentanyl sublingual tablets (Abstral)

Fentanyl nasal spray (Lazanda)

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 transmucosal is indicated only for the management of breakthrough cancer pain in patients with malignancies 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, for one week or longer:

- at least 60 mg oral morphine/day,
- at least 25 mcg 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.

Fentanyl citrate transmucosal 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.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, fentanyl citrate 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 intermittent or “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 in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. 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.

The substitution of Actiq, Fentora, Onsolis, Abstral, or Lazanda for any other fentanyl product may result in fatal overdose. When prescribing, do not convert patients on a mcg per mcg basis from one transmucosal fentanyl product to another. Carefully consult approved dosing recommendations. When dispensing, do not substitute one transmucosal fentanyl prescription for other transmucosal fentanyl products. Substantial differences exist in the pharmacokinetic profile of the transmucosal fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of one fentanyl product for any other fentanyl product may result in fatal overdose.

RATIONALE:

These fentanyl citrate 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.

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.

- 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.

DOSAGE AND ADMINISTRATION

Fentanyl buccal soluble film (Onsolis)

- **Initial dosing:** Individually titrate Onsolis to a dose that provides adequate analgesia with tolerable side effects. All patients MUST begin treatment using one 200 mcg Onsolis film. Due to differences in pharmacokinetic properties and individual variability, patients switching from another transmucosal fentanyl product must be started on no greater than 200 mcg of Onsolis.
- **Increasing the dose:** If adequate pain relief is not achieved after one 200 mcg Onsolis film, titrate using multiples of the 200 mcg Onsolis film (for doses of 400, 600, or 800 mcg). Increase the dose by 200 mcg in each subsequent episode until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Do not use more than four of the 200 mcg Onsolis films simultaneously. When multiple 200 mcg Onsolis films are used, they should not be placed on top of each other and may be placed on both sides of the mouth.
- If adequate pain relief is not achieved after 800 mcg (i.e., four 200 mcg Onsolis films), and the patient has tolerated the 800 mcg dose, treat the next episode by using one 1200 mcg Onsolis film. Doses above 1200 mcg Onsolis should not be used.
- **Maintenance:** Once adequate pain relief is achieved with a dose between 200 and 800 mcg, the patient should use or safely dispose of all remaining 200 mcg Onsolis films. Patients who require 1200 mcg should dispose of all remaining unused 200 mcg Onsolis films. The patient should then get a prescription for Onsolis films of the dose determined by titration (i.e., 200, 400, 600, 800, or 1200 mcg) to treat subsequent episodes.
- **Single doses should be separated by at least 2 hours. Onsolis should only be used once per breakthrough cancer pain episode, i.e., Onsolis should not be redosed within an episode.**
- **Dosage adjustment:** During maintenance treatment, if the prescribed dose no longer adequately manages the breakthrough cancer pain episode for several consecutive episodes, increase the dose of Onsolis as described above (*Increasing the dose*). Once a successful dose has been found, each episode is treated with a single film. Onsolis should be limited to four or fewer doses per day. Consider increasing the dose of the

around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

- **Administration of Onsolis:** Use the tongue to wet the inside of the cheek or rinse the mouth with water to wet the area for placement of Onsolis. Open the Onsolis package immediately prior to product use. Place the entire film near the tip of a dry finger with the pink side facing up and hold in place. Place the pink side of the Onsolis film against the inside of the cheek. Press and hold the film in place for 5 seconds. The film should stay in place on its own after this period. Liquids may be consumed after 5 minutes
- The Onsolis film will dissolve within 15 to 30 minutes after application. The film should not be manipulated with the tongue or finger(s) and eating food should be avoided until the film has dissolved.
- The Onsolis film should not be cut or torn, and if chewed and swallowed might result in lower concentrations than when used as directed.

DOSAGE AND ADMINISTRATION

Fentanyl sublingual tablets (Abstral)

- **Initial dosing:** Begin titration of **all** patients with an initial dose of Abstral of 100 mcg. Due to differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl containing products to Abstral must start with the 100 mcg dose.
- If adequate analgesia is not obtained after Abstral, the patient may use a second Abstral dose (after 30 minutes) as directed by their health care provider. No more than two doses of Abstral may be used to treat an episode of breakthrough pain, Patients must wait at least 2 hours before treating another episode of breakthrough pain with Abstral.
- **Increasing the dose:** If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved.
- Increase the dose by 100 mcg multiples up to 400 mcg as needed. If adequate analgesia is not obtained with a 400 mcg dose, the next titration step is 600 mcg.
- If adequate analgesia is not obtained with a 600 mcg dose, the next titration step is 800 mcg. The efficacy and safety of doses higher than 800 mcg have not been evaluated in clinical studies in patients.
- During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
- If adequate analgesia is not obtained 30 minutes after the use of Abstral, the patient may repeat the same dose of Abstral. No more than two doses of Abstral may be used to treat an episode of breakthrough pain.
- **Maintenance:** Once an appropriate dose for pain management has been established, instruct patients to use only one Abstral tablet of the appropriate strength per dose. Maintain patients on this dose.
- If adequate analgesia is not obtained after use of Abstral, the patient may use a second Abstral dose (after 30 minutes) as directed by their health care provider. No more than two doses of Abstral may be used to treat an episode of breakthrough pain. Patients must wait at least 2 hours before treating another episode of breakthrough pain with Abstral.
- If more than four episodes of breakthrough pain are experienced per day, re-evaluate the dose of the long-acting opioid used for persistent underlying cancer pain. If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the Abstral dose as necessary to ensure the patient is on an appropriate dose.
- Limit the use of Abstral to treat four or fewer episodes of breakthrough pain per day.
- It is imperative that any dose re-titration is monitored carefully by a healthcare professional.

- **Tablet Administration:** Place Abstral tablets on the floor of the mouth directly under the tongue immediately after removal from the blister unit. Do not chew, suck, or swallow Abstral tablets. Allow Abstral tablets to completely dissolve in the sublingual cavity. Advise patients not to eat or drink anything until the tablet is completely dissolved.
- **Discontinuation of Therapy:** For patients no longer requiring opioid therapy, consider discontinuing Abstral along with a gradual downward titration of other opioids to minimize possible withdrawal effects.
- In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, Abstral therapy can usually be discontinued immediately.

DOSAGE AND ADMINISTRATION

Fentanyl nasal spray (Lazanda)

Open the child-resistant container just prior to product use and **always replace the bottle in the child-resistant container between doses.**

The dose of Lazanda is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by dose titration.

- **Starting Dose:** Begin treatment of **all** patients (including those switching from another fentanyl product) using ONE 100 mcg spray of Lazanda (1 spray in one nostril). Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product.
- If adequate analgesia is obtained within 30 minutes of administration of the 100 mcg single spray, treat subsequent episodes of breakthrough pain with this dose.
- **Titration steps:** If adequate analgesia *is not achieved* with the first 100 mcg, dose, dose escalate in a step-wise manner over consecutive episodes of breakthrough pain until adequate analgesia with tolerable side effects is achieved.
- Patients **MUST** wait at least 2 hours before treating another episode of breakthrough cancer pain with Lazanda.
- **The titration steps should be:**

Lazanda Dose	Using
100 mcg	1 x 100 mcg spray
200 mcg	2 x 100 mcg spray (1 in each nostril)
400 mcg	1 x 400 mcg spray
800 mcg	2 x 400 mcg spray (1 in each nostril)

- Patients should confirm the dose of Lazanda that works for them with a second episode of breakthrough pain and review their experience with their physicians to determine if that dose is appropriate, or whether a further adjustment is warranted
- The safety and efficacy of doses higher than 800 mcg have not been evaluated in clinical studies. There are no clinical data to support the use of a combination of dose strengths to treat an episode.
- **Maintenance Treatment:** Once an appropriate dose has been established, instruct patients to use that dose for each subsequent breakthrough cancer pain episode. Limit Lazanda use to four or fewer doses per day.
- **Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with Lazanda.**
- During any episode of breakthrough cancer pain, if there is inadequate pain relief after 30 minutes following Lazanda dosing or if a separate episode of breakthrough cancer pain occurs before the next dose of Lazanda is permitted (i.e. within 2 hours), the patients may use a rescue medication as directed by their healthcare provider.

- **Dose Re-Adjustment:** If more than four episodes of breakthrough pain are experienced per day, re-evaluate the dose of the long-acting opioid used for persistent underlying cancer pain. If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the Lazanda dose as necessary to ensure the patient is on an appropriate dose.
- Limit the use of Lazanda to treat four or fewer episodes of breakthrough pain per day.

- **Administration of Lazanda**

Instruct patients on the proper use of Lazanda.

1. Prime the device before use by spraying into the pouch (4 sprays in total).
2. Insert the nozzle of the Lazanda bottle a short distance (about ½ inch or 1 cm) into the nose and point towards the bridge of the nose, tilting the bottle slightly.
3. Press down firmly on the finger grips until they hear a “click” and the number in the counting window advances by one.

Advise patients that the fine mist spray is not always felt on the nasal mucosal membrane and to rely on the audible click and the advancement of the dose counter to confirm a spray has been administered

- **Discontinuation of Therapy:** For patients no longer requiring opioid therapy, consider discontinuing Lazanda along with a gradual downward titration of other opioids to minimize possible withdrawal effects.
- In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, Lazanda therapy can usually be discontinued immediately.

DRUG INTERACTIONS

- **CYP3A4 inhibitors:** The concomitant use of transmucosal fentanyl with CYP3A4 inhibitors (e.g, ritonavir, ketoconazole, itraconazole fluconazole, troleandomycin, clarithromycin, erythromycin, telithromycin, indinavir, saquinavir, nelfinavir, nefazodone, amprenavir, fosamprenavir, aprepitant, diltiazem 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 CYP3A4 inhibitors, or for whom the dose of a CYP3A4 inhibitor is being increased, 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 (decrease fentanyl plasma concentrations). Patients who stop therapy with, or decrease the dose of, CYP3A4 inducers may experience a sudden increase in fentanyl plasma concentrations.
- **MAO inhibitors:** Concomitant use of fentanyl citrate with an MAO inhibitor, or within 14 days of discontinuation, is not recommended.
- **Drug treatment of allergic rhinitis (Lazanda only):** In view of the possibility that the titration of a patient while they are experiencing an acute episode of rhinitis could lead to incorrect dose identification (particularly if they are using a vasoconstrictive decongestant), titration under these circumstances must be avoided.

ADDITIONAL DRUG INFORMATION:

- Cephalon Medical Services (Actiq, Fentora)
Phone: 1-800-896-5855;
Actiq & Fentora REMS 1-888-688-6885 or www.actiqandfentorarems.com
- Meda Pharmaceuticals (Onsolis)
Phone: 1-800-526-3840; Onsolis FOCUS 1-877-466-7654 or www.OnsolisFocus.com
- ProStrakan, Inc. (Abstral)

Phone: 1-888-227-8725; Abstral REMS 1-888-227-8725 or www.abstralrems.com

- Archimedes Pharma (Lazanda)

Phone: 1-866-435-6775; Lazanda REMS 1-855-841-4234 or www.LazandaREMS.com

References:

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

Fentora (fentanyl citrate). Product Information. Cephalon. 2009.

Onsolis (fentanyl citrate). Product Information. Meda Pharmaceuticals. 2009.

Abstral (fentanyl). Product Information. ProStrakan, Inc. 2011.

Lazanda (fentanyl). Product Information. Archimedes Development Ltd. 2011.