DOSAGE AND ADMINISTRATION

- Patients must require and use around-the-clock opioids when taking ACTIQ. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initial dose of ACTIQ: 200 mcg. Prescribe an initial supply of six 200 mcg ACTIQ units. (2.2)
- Individually titrate to a tolerable dose that provides adequate analgesia using single dose per breakthrough pain episode. (2.2)
- No more than two doses can be taken per breakthrough pain episode. (2.3, 2.4)
- Wait at least 4 hours before treating another episode of breakthrough pain with ACTIQ. (2.3, 2.4)
- Limit consumption to four or fewer units per day once successful dose is found. (2.2)
- When opioid therapy is no longer required, consider discontinuing ACTIQ along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.6)

DOSE FORMS AND STRENGTHS

- Solid oral transmucosal lozenge: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Significant respiratory depression. (4)
- Management of acute or postoperative pain including headache/migraines and dental pain. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of ACTIQ. (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.1)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ACTIQ in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ACTIQ in patients with impaired consciousness or coma. (5.13)

ADVERSE REACTIONS

Most common (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache, dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid the use of mixed agonist/antagonist or partial agonist analgesics in patients who are already receiving a full opioid agonist analgesic (including ACTIQ) because they may reduce analgesic effect of ACTIQ or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Renal and Hepatic Impairment: Administer ACTIQ with caution. (8.6)

Revised: 10/2019

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

5.14 Risks of Use in Patients with Gastrointestinal Conditions
5.15 Increased Risk of Seizures in Patients with Seizure Disorders
5.16 Risks of Driving and Operating Machinery
5.17 Cardiac Disease

6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal or Hepatic Impairment
8.7 Sex

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; AND NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression
Serious, life-threatening and/or fatal respiratory depression has occurred in patients treated with ACTIQ, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of ACTIQ or following a dose increase [see Warnings and Precautions (5.1)]. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose [see Warnings and Precautions (5.2)]. Due to the risk of respiratory depression, ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients [see Contraindications (4)].

Accidental Ingestion
Accidental ingestion of even one dose of ACTIQ, especially by children, can result in a fatal overdose of fentanyl [see Warnings and Precautions (5.2)]. Death has been reported in children who have accidentally ingested ACTIQ. ACTIQ must be kept out of reach of children [see Patient Counseling Information and How Supplied/Storage and Handling (16)].

Cytochrome P450 3A4 Interaction
The concomitant use of ACTIQ with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving ACTIQ and any CYP3A4 inhibitor or inducer [see Warnings and Precautions (5.3), Drug Interactions (7)].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.4), Drug Interactions (7)].

• Reserve concomitant prescribing of ACTIQ and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

Risk of Medication Errors
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 and that could result in fatal overdose [see Dosage and Administration (2.1), Warnings and Precautions (5.5)].

• When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ACTIQ [see Dosage and Administration (2.1)].
• When dispensing, do not substitute an ACTIQ prescription for other fentanyl products.

ACTIQ exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing ACTIQ, and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.6)].

Risk Evaluation and Mitigation Strategy (REMS) Access Program
Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program [see Warnings and Precautions (5.7)]. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-922-1483.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of ACTIQ during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.8)].

1 INDICATIONS AND USAGE
ACTIQ is indicated for the management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Limitations of Use:
• Not for use in opioid non-tolerant patients.
• Not for use in the management of acute or postoperative pain, including headache/migraine and dental pain [see Contraindications (4)].
• As a part of the TIRF REMS Access program, ACTIQ may be dispensed only to outpatients enrolled in the program [see Warnings and Precautions (5.7)]. For inpatient administration of ACTIQ (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage and Administration Instructions
• Healthcare professionals who prescribe ACTIQ on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of ACTIQ [see Warnings and Precautions (5.7)].
• Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].
• It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
• Initiate the dosing regimen for each patient individually, taking into account the patient’s severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5)].
2.4 Maintenance Dosing
a. Once titrated to an effective dose, patients should generally use ONLY ONE ACTIQ unit of the appropriate strength per breakthrough pain episode.
b. On those occasions when the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patient may take ONLY ONE additional dose using the same strength for that episode.
c. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain.
d. Dosage adjustment of ACTIQ may be required in some patients in order to continue to provide adequate relief of breakthrough pain.
e. Generally, the ACTIQ 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.
f. 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.

2.5 Administration of ACTIQ
Open the blister pack with scissors immediately prior to product use. 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. If a patient's blood pressure drops or if breakthrough pain is not relieved, the ACTIQ unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in ACTIQ clinical trials. 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.

2.6 Discontinuation of ACTIQ
When opioid therapy is no longer required, consider discontinuing ACTIQ along with a gradual downward tapering (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, ACTIQ therapy can usually be discontinued immediately. [See Drug Abuse and Dependence (9.3)].

2.7 Disposal of ACTIQ
After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.

• If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
• Dispose of handles in the child-resistant container (as described in steps 1 and 2) at least once a day.
• If the temporary storage bottle provided as part of the ACTIQ Child Safety Kit is available, partially consumed units may be stored in the specially provided child-resistant container out of the reach of children until proper disposal is possible. Unopened units remaining from a prescription must be properly disposed as soon as they are no longer needed.

To dispose of the unused ACTIQ units:
• Remove the ACTIQ unit from its blister package using scissors, and hold ACTIQ by its handle over the toilet bowl.
• Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
• Dispose of the handle in a place that is out of the reach of children.
• Repeat steps 1, 2, and 3 for each ACTIQ unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.
• Do not flush the entire ACTIQ units, ACTIQ handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it.

In the event that a caregiver requires additional assistance in disposing of excess unused units that remain in the first dose after a patient has expired, instruct them to call the toll-free number for Teva Pharmaceuticals (1-888-483-8279) or seek assistance from their local DEA office.

3. DOSAGE FORMS AND STRENGTHS
Solid oral transmucosal lozenge: Each dosage unit has white to off-white color and is a solid drug matrix on a handle. Each strength is marked on the individual solid drug matrix and the handle tag. ACTIQ is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths [see How Supplied/Storage and Handling (16)].

4. CONTRAINDICATIONS
ACTIQ is contraindicated in:
• Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients. [See Indications and Usage (1.1), Warnings and Precautions (5.1), Adverse Reactions (6.2)].
• Significant respiratory depression [see Warnings and Precautions (5.1)].
• Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department.
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.8)].
• Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.9)].
• Known hypersensitivity to fentanyl or components of ACTIQ (e.g., anaphylaxis, hypersensitivity) [see Adverse Reactions (6.2)].

5. WARNINGS AND PRECAUTIONS
5.1 Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ACTIQ, the risk is greatest during the initiation of therapy due to a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ACTIQ.

To reduce the risk of respiratory depression, proper dosing and titration of ACTIQ are essential [see Dosage and Administration (2)]. Overestimating the ACTIQ dosage can result in a fatal overdose with the first dose. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose [see Warnings and Precautions (5.5)]. ACTIQ could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.
 Accidental ingestion of even one dose of ACTIQ, especially by children, can result in respiratory depression and death due to an overdose of fentanyl [see Warnings and Precautions (5.1, 5.2)].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see Dosage and Administration (2.6)]. ACTIQ should always be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [see Dosage and Administration (2.3)].

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested ACTIQ. Patients and their caregivers must be informed that ACTIQ contains a medicine in an amount and concentration sufficient to cause serious harm or death to children. Healthcare providers, dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full-time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Patients should be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [see Patient Counseling Information (17)].

Detailed instructions for proper storage, administration, disposal, and important instructions for managing an overdose of ACTIQ are provided in the ACTIQ Medication Guide. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Substrates

Concomitant use of ACTIQ with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see Warnings and Precautions (5.4)]. When using ACTIQ with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, such as rifampin, carbamazepine, and phenytoin, in ACTIQ-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using ACTIQ with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ACTIQ-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ACTIQ until stable drug effects are achieved [see Drug Interactions (7)].

Concomitant use of ACTIQ with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using ACTIQ with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see Drug Interactions (7)].

5.4 Risk of Respiratory Depression

Respiratory depression is the principal risk of ACTIQ. Respiratory depression is more frequent in patients who are older than 65 years of age or in patients with concomitant CNS depressant use. Respiratory depression, including the development of respiratory arrest and death, has been associated with the use of ACTIQ in these patients.

Respiratory depression occurs as a result of opioid antagonism of the brain's opioid receptors, which are involved in the regulation of the sleep/wake cycle, muscle tone, and respiration. Antagonism of these receptors can cause respiratory depression, including respiratory arrest and death, in patients with baseline respiratory impairment (e.g., chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Use ACTIQ with caution in patients with these conditions. Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.1)].

Monitor such patients closely, particularly when initiating and titrating ACTIQ and when ACTIQ is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.1)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of ACTIQ with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and

ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

5.4  Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

[see Drug Interactions (7)]

Increasing the opioid dosage if needed to maintain adequate analgesia or if dependence to fentanyl. When using ACTIQ with CYP3A4 inducers or discontinuing or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using ACTIQ with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ACTIQ-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ACTIQ until stable drug effects are achieved [see Drug Interactions (7)].

Concomitant use of ACTIQ with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using ACTIQ with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see Drug Interactions (7)].

5.4 Risk of Respiratory Depression

Respiratory depression is the principal risk of ACTIQ. Respiratory depression is more frequent in patients who are older than 65 years of age or in patients with concomitant CNS depressant use. Respiratory depression, including the development of respiratory arrest and death, has been associated with the use of ACTIQ in these patients.

Respiratory depression occurs as a result of opioid antagonism of the brain's opioid receptors, which are involved in the regulation of the sleep/wake cycle, muscle tone, and respiration. Antagonism of these receptors can cause respiratory depression, including respiratory arrest and death, in patients with baseline respiratory impairment (e.g., chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression). Use ACTIQ with caution in patients with these conditions. Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.1)].

Monitor such patients closely, particularly when initiating and titrating ACTIQ and when ACTIQ is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.1)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of ACTIQ with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and
ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

norpethidine reuptake inhibitors (SNRs), tricyclic antidepressants (TCAs), trignetics, S-HT3 receptors. Drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see Drug Interactions (7)]. This may occur within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue ACTIQ if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include hypotension and/or hypotension, and may increase the risk of seizures occurring in other clinical settings (e.g., intracranial pressure, brain tumors, or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or monoamine oxidase inhibitors) [see Drug Interactions (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ACTIQ. In patients with circulatory shock, ACTIQ may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ACTIQ in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury
In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ACTIQ may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ACTIQ. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ACTIQ in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions
ACTIQ is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The fentanyl in ACTIQ may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders
The fentanyl in ACTIQ may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during ACTIQ therapy.

5.16 Risks of Driving and Operating Machinery
ACTIQ may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ACTIQ and know how they will react to the medication.

5.17 Cardiac Disease
Intravenous fentanyl may produce bradycardia. Therefore, use ACTIQ with caution in patients with bradyarrhythmias.

6 ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression [see Warnings and Precautions (5.1)]
- Interactions with Benzodiazepines and Other CNS Depressants [see Warnings and Precautions (5.4)]
- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.6)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.8)]
- Serotonin Syndrome [see Warnings and Precautions (5.10)]
- Adrenal Insufficiency [see Warnings and Precautions (5.11)]
- Severe Hypotension [see Warnings and Precautions (5.12)]
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.14)]
- Seizures [see Warnings and Precautions (5.15)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ACTIQ has been evaluated in 257 opioid-tolerant chronic cancer pain patients. The duration of ACTIQ use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

The most serious adverse reactions associated with ACTIQ are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.

Because the clinical trials of ACTIQ were designed to evaluate safety and efficacy in treating breakthrough cancer pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse event among patients who received ACTIQ for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of ACTIQ therapy, or cancer-related symptoms.

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. Table 1, lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schemes used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1. Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Titration (Events in 1% or More of Patients)

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-600 mcg</td>
<td>120-1400 mcg</td>
</tr>
<tr>
<td>(n=230)</td>
<td>(n=138)</td>
</tr>
<tr>
<td>1600 mcg</td>
<td>&gt;1600 mcg</td>
</tr>
<tr>
<td>(n=54)</td>
<td>(n=41)</td>
</tr>
</tbody>
</table>

Body As a Whole

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Dose* (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>6 4 0 7 9</td>
</tr>
<tr>
<td>Headache</td>
<td>3 4 6 5 6</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 2 0 0 4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 16 11 15 17</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10 9 11 20 17</td>
</tr>
<tr>
<td>Confusion</td>
<td>1 6 2 0 4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 0 2 0 3</td>
</tr>
<tr>
<td>Abnormal Gait</td>
<td>0 1 4 0 2</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1 1 2 0 2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1 1 0 0 2</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>2 0 2 0 2</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0 1 2 2 1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 1 2 0 1</td>
</tr>
<tr>
<td>Thinking Abnormal</td>
<td>0 1 0 1 0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 0 0 0 1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 3 6 5 4</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 0 0 5 2</td>
</tr>
<tr>
<td>Rash</td>
<td>1 1 0 2 2</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 1 2 2 2</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>1 0 2 0 2</td>
</tr>
</tbody>
</table>

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following adverse reactions not reflected in Table 1 occurred during titration with an overall frequency of 0.5% or greater and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, abdominal pain, chills, back pain, chest pain, infection

Dyspnea: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervousness: Hypotension, hypoglycemia

Respiratory: Pharyngitis, cough increased

The following reactions occurred during titration with an overall frequency of less than 1% and are listed in descending order of frequency within each body system.

Body as a Whole: Bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Dyspepsia: Ectopic, falciparum impaction, gum hemorrhage, mouth ulceration, oral moniliasis
**ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII**

- **Hemato and Lymphatic:** Anemia, leukopenia
- **Metabolic and Nutritional:** Edema, hypercalcemia, weight loss
- **Musculoskeletal:** Myalgia, pathological fracture, myasthenia

**Nervous:** Abnormal dreams, urinary retention, agitation, amnesia, emotional lability, euphoria, incoordination, libido decreased, neuropathy, paresthesia, speech disorder

**Respiratory:** Hemoptysis, pleural effusion, rhinitis, asthma, hiccup, pneumonia, respiratory insufficiency, sputum increased

**Skin and Appendages:** Alopoea, exfoliative dermatitis

**Special Senses:** Taste perversion

**Urogenital:** Vaginal hemorrhage, dysuria, hematuria, urinary incontinence, urinary tract infection

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 2 lists by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during the long-term extension study. Adverse reactions are listed in descending order of frequency within each body system.

### Table 2. Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment (Events in 1% or More of Patients)

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200-600 mcg (n=98)</td>
</tr>
<tr>
<td>Body As A Whole</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>25</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>4</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
</tr>
<tr>
<td>Intestinal Obstruction</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Nervous</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8</td>
</tr>
<tr>
<td>Confusion</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal Gait</td>
<td>5</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>3</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
</tr>
<tr>
<td>Stupor</td>
<td>4</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>1</td>
</tr>
<tr>
<td>Thinking Abnormal</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>1</td>
</tr>
<tr>
<td>Convulsion</td>
<td>0</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
</tr>
<tr>
<td>Sweating</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>2</td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>1</td>
</tr>
</tbody>
</table>

*Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.
**Clinical Impact:** The concomitant use of ACTIQ and CYP3A4 inducers can decrease the plasma concentration of fentanyl [see Clinical Pharmacology (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl [see Warnings and Precautions (5.3)]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase [see Clinical Pharmacology (12.3)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

**Examples:** Rifampin, carbamazepine, phenytoin

### Benzodiazepines and Other CNS Depressants

**Clinical Impact:** Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

**Intervention:** Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see Warnings and Precautions (5.4)].

**Examples:** Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

### Serotonergic Drugs

**Clinical Impact:** The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see Warnings and Precautions (5.10)].

**Intervention:** If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ACTIQ if serotonin syndrome is suspected.

**Examples:** Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin-norepinephrine neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

### Monoamine Oxidase Inhibitors (MAOIs)

**Clinical Impact:** MAOIs that appear to be less likely to interact with opioids include clorgyline and tranylcypromine. Short-acting MAOIs have a lower risk of serotonin toxicity than longer-acting MAOIs. MAOIs may require dose reduction when used with opioids [see Warnings and Precautions (5.1)].

**Intervention:** The use of ACTIQ is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

**Examples:** Phenelzine, tranylcypromine, linezolid

### Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

**Clinical Impact:** May reduce the analgesic effect of ACTIQ and/or precipitate withdrawal symptoms.

**Intervention:** Avoid concomitant use.

**Examples:** Butorphanol, nalbuphine, pentazocine, buprenorphine

### Muscle Relaxants

**Clinical Impact:** Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Intervention:** Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ACTIQ and/or the muscle relaxant as necessary.

### Diuretics

**Clinical Impact:** Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

**Intervention:** Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

### Anticholinergic Drugs

**Clinical Impact:** The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**Intervention:** Monitor patients for signs of urinary retention or reduced gastric motility when ACTIQ is used concomitantly with anticholinergic drugs.

### Pregnancy

#### Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome in patients who have developed physical dependence to opioids [see Warnings and Precautions (5.8)]. Available data with ACTIQ in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. When administered during gestation through lactation, fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations was noted in animal studies completed to date [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

#### Clinical Considerations

**Fetal/Neonatal Adverse Reactions**

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.8)].

**Labor or Delivery**

Opioids cross the placenta and may produce respiratory depression and physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate.

ACTIQ is not recommended for use in pregnant women during or immediately prior to labor, when less toxic analgesic techniques are more appropriate. Opioid analgesics, including ACTIQ, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

#### Data

**Human Data**

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

**Animal Data**

Fentanyl (25, 50, or 100 mcg/kg) citrate was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6 to 17). Maternal toxicity was noted at doses >100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 3.5 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses >100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 3.5 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison). Fentanyl has been shown to be embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.2 times the 1600 mcg dose of ACTIQ on a mg/m2 basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (1 times the 1600 mcg dose of ACTIQ based on a mg/m2 basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneous implants of osmotic minipumps at gd 8, 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 3 times the human dose of 1600 mcg ACTIQ per pain episode on a mg/m2 basis and produced mean steady-state plasma levels that are 3.4 times higher than the mean Cmax observed following administration of 1600 mcg dose of ACTIQ in humans.
in a postnatal development study, pregnant rats were treated with GD 6 through Lactation Day (L) 20 at oral doses of fentanyl (25, 50, 100, and 400 mcg/kg). Maternal toxicity was noted at doses >100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at >100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at L 4 was reduced to 48% at 400 mcg/kg and by L 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is 0.6 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison.

8.2 Lactation

Risk Summary

Fentanyl is excreted in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ACTIQ.

Clinical Considerations

Monitor infants exposed to ACTIQ through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (15.1)].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below 16 years of age have not been established.

In a clinical study, 15 opioid-tolerant pediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with ACTIQ. The study was too small to allow conclusions on safety and efficacy in this patient population. Twelve of the fifteen opioid-tolerant children and adolescents aged 5 to 15 years in this study received ACTIQ at doses ranging from 200 mcg to 600 mcg. The mean (CV%; range) dose-normalized (to 200 mcg) Cmax and AUC0-8 values were 0.87 ng/mL (51%; 0.42-1.30) and 4.54 ng •h/mL (42%; 2.37-6.0), respectively, for children ages 5 to <11 years old (N = 3) and 0.68 ng/mL (72%; 0.15-1.44) and 6.38 (192%; 0.84-50.78), respectively, for children ages 11 to ≥16 years (N = 9).

8.5 Geriatric Use

Of the 257 patients in clinical studies of ACTIQ in breakthrough cancer pain, 61 (24%) were 65 years of age or older, while 15 (6%) were 75 years of age or older. Those patients over the age of 65 years were titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in ACTIQ clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, exercise caution when individually titrating ACTIQ in elderly patients to provide adequate efficacy while minimizing risk.

8.6 Patients with Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of ACTIQ in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isozyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolic route of fentanyl metabolism.

8.7 Sex

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant sex differences were noted either in dosage requirement or in observed adverse reactions.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ACTIQ contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

ACTIQ contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine oxycodone, oxymorphone, and tapentadol. ACTIQ can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.6)].
ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

11 DESCRIPTION
ACTIQ (fentanyl citrate) oral transmucosal lozenge is a solid formulation of fentanyl, an opioid agonist, intended for oral transmucosal administration. ACTIQ is formulated as a white to off-white solid drug matrix on a handle that is fracture resistant (ABS plastic) under normal conditions when used as directed. ACTIQ is designed to be dissolved slowly in the mouth to facilitate transmucosal absorption. The handle allows the ACTIQ unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

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 \( \phi \text{L} \) 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:

\[
\text{CH}_3\text{CH}_2\text{CON}\cdot\text{N-CH}_3\text{CH}_3\cdot\text{COOH} = \text{HO} = \text{CH}_2\text{COOH}
\]

Inactive Ingredients: Hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner’s sugar).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Fentanyl is an opioid agonist whose principal therapeutic action is analgesia. 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 a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and electrical stimulation. 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). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
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 in the small intestine is delayed 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 biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating, and/or orthostatic hypotension.

Effects on the Endocrine System
Opioids inhibit the secretion of adenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Adverse Reactions (6.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [see Adverse Reactions (6.2)]. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
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. The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.
**ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII**

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving 200, 400, 800, and 1600 mcg Units of ACTIQ

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>200 mcg</th>
<th>400 mcg</th>
<th>800 mcg</th>
<th>1600 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tmax, minute (median range)</strong></td>
<td>40 (20-120)</td>
<td>25 (20-240)</td>
<td>25 (20-120)</td>
<td>20 (20-480)</td>
</tr>
<tr>
<td><strong>Cmax, ng/mL mean (%CV)</strong></td>
<td>0.39 (23)</td>
<td>0.75 (33)</td>
<td>1.55 (30)</td>
<td>2.51 (23)</td>
</tr>
<tr>
<td><strong>AUC0-1440, ng/mL minute mean (%CV)</strong></td>
<td>102 (65)</td>
<td>243 (67)</td>
<td>573 (64)</td>
<td>1026 (67)</td>
</tr>
<tr>
<td><strong>t1/2, minute mean (%CV)</strong></td>
<td>193 (48)</td>
<td>386 (115)</td>
<td>381 (55)</td>
<td>358 (45)</td>
</tr>
</tbody>
</table>

*Based on arterial blood samples.

**Distribution**

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. 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 free fraction of fentanyl increases with acidoses. The mean volume of distribution at steady state (Vss) was 4 L/kg.

**Elimination**

The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after ACTIQ administration is about 7 hours.

**Metabolism**

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isomor. Norfentanyl was not found to be pharmacologically active in animal studies (see Drug Interactions (7)).

**Excretion**

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the 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.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed. Doses are equivalent to 1.13 and 2.7 times the exposure of a single human dose of 1600 mcg per pain episode, respectively, based on an AUC comparison. In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis

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

**Impairment of Fertility**

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 4.0-times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decrease percent mobile sperm, decreased sperm concentration as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 2.7 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison. Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 1600 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for ACTIQ.

**14 CLINICAL STUDIES**

ACTIQ was investigated in clinical trials involving 257 opioid tolerant adult cancer patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in cancer patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects. In these studies 11% of patients withdrew due to adverse reactions and 14% withdrew due to other reasons.

The successful dose of ACTIQ for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and is thus best determined by dose titration.

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of ACTIQ for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 5.

**ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII**

Table 5. Successful Dose of ACTIQ Following Initial Titration

**ACTIQ Dose** | Total No. (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mcg</td>
<td>13 (14)</td>
</tr>
<tr>
<td>400 mcg</td>
<td>19 (21)</td>
</tr>
<tr>
<td>600 mcg</td>
<td>14 (15)</td>
</tr>
<tr>
<td>800 mcg</td>
<td>18 (20)</td>
</tr>
<tr>
<td>1200 mcg</td>
<td>13 (14)</td>
</tr>
<tr>
<td>1600 mcg</td>
<td>15 (16)</td>
</tr>
</tbody>
</table>

Mean ± SD 759 ± 468 mcg

On average, patients over 65 years of age titrated to a mean dose that was about 200 mcg less than the mean dose to which younger adult patients were titrated.

ACTIQ was administered beginning at Time 0 minutes and produced more pain relief compared with placebo at 15, 30, 45, and 60 minutes as measured after the start of administration (see Figure 2). The differences were statistically significant.

**Figure 2. Pain Relief (PR) Scores (Means±SD) During the Double-Blind Phase – All Patients with Evaluable Episodes on Both ACTIQ and Placebo (N=86)**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

ACTIQ is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose. Each dosage unit has a white to off-white color. Each individual opioid drug matrix is marked with “ACTIQ” and the strength of the unit (“200”, “400”, “600”, “800”, “1200”, or “1600”). The dosage strength is also marked on the handle tag, the blister package and the carton. See blister package and carton for product information.

**16.1 Dosage Strength (fentanyl base)**

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Carton/Blister Package Color</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mcg</td>
<td>Gray</td>
<td>NDC 63459-502-30</td>
</tr>
<tr>
<td>400 mcg</td>
<td>Blue</td>
<td>NDC 63459-504-30</td>
</tr>
<tr>
<td>600 mcg</td>
<td>Orange</td>
<td>NDC 63459-506-30</td>
</tr>
<tr>
<td>800 mcg</td>
<td>Purple</td>
<td>NDC 63459-508-30</td>
</tr>
<tr>
<td>1200 mcg</td>
<td>Green</td>
<td>NDC 63459-512-30</td>
</tr>
<tr>
<td>1600 mcg</td>
<td>Burgundy</td>
<td>NDC 63459-516-30</td>
</tr>
</tbody>
</table>

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

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.) Protect ACTIQ from freezing and moisture. Do not use if the blister package has been opened. Store ACTIQ securely and dispose of properly [see Patient Counseling Information (17)].

**17 PATIENT COUNSELING INFORMATION**

Advised the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal of Unused and Used ACTIQ [see Medication Guide / Instructions for Use].

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store ACTIQ securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see Warnings and Precautions (5.1, 5.6), Drug Abuse and Dependence (9.2)]. Inform patients that leaving ACTIQ unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Disposal of Used ACTIQ Units

Instruct patients on proper disposal of completely used and partially used ACTIQ units as follows:

1. If any of the drug remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, then dispose of the handle in a trash container that is out of the reach of children.

2. If any of the drug remains on the handle, throw away the handle in a trash container that is out of the reach of children.
3. Dispose of handles in the child-resistant container (as described in steps 1 and 2) at least once a day. If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the ACTIQ unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible. Disposal of the ACTIQ Units: When Interfered Needed: Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed. To dispose of the unused ACTIQ units:
• Remove the ACTIQ unit from its blister package using scissors, and hold within the ACTIQ by its handle over the toilet bowl.
• Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
• Dispose of the handle in a place that is out of the reach of children.
• Repeat steps 1, 2, and 3 for each ACTIQ unit. Flush the toilet twice after 5 instants have been used and reused into the toilet.
Do not flush the entire ACTIQ units. ACTIQ handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it. Detailed instructions for the proper storage, administration, disposal, and interim storage containers to help patients store ACTIQ and other medicines out of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for Teva Pharmaceuticals (1-888-483-8279) or seek assistance from their local DEA office.

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting ACTIQ or when the dosage is increased, and that it can occur even at recommended dosages [see Warnings and Precautions (5.1)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion
• Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure [see Warnings and Precautions (5.2)].
• Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death [see Warnings and Precautions (5.2)].
• Instruct patients to store ACTIQ securely and to dispose of unused ACTIQ [see Warnings and Precautions (5.2, 5.7), Patient Counseling Information, Disposal of Unused ACTIQ Units].
• Instruct patients and caregivers to keep both used and unused ACTIQ out of the reach of children [see Warnings and Precautions (5.2)].
• Instruct patients and their caregivers that, in the event that a unit is not completely consumed, it must be properly disposed as soon as possible [see Warnings and Precautions (5.2, 5.7), Patient Counseling Information, Disposal of Unused ACTIQ Units].

ACTIQ Child Safety Kit
Provides parents and their caregivers who have children in the home or visiting with an ACTIQ Child Safety Kit, which contains educational materials and safe interim storage containers to help patients store ACTIQ and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, health care professionals can call 1-888-534-3119.

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)
Inform patients and caregivers that potentially fatal additive effects may occur if ACTIQ is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see Warnings and Precautions (5.4), Drug Interactions (7)].

Addiction, Abuse, and Misuse
Inform patients that the use of ACTIQ, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see Warnings and Precautions (5.6)]. Instruct patients not to share ACTIQ with others and to take steps to protect ACTIQ from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS
Advises patients of the following information pertaining to the TIRF REMS:
• Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive ACTIQ.
• Allowing patients the opportunity to ask questions and discuss any concerns regarding ACTIQ in the TIRF REMS Access program.
As required by the TIRF REMS Access program, review the contents of the ACTIQ Medication Guide with every patient before initiating treatment with ACTIQ.
• Advise the patient that ACTIQ is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug.
• Advise the patient that only enrolled healthcare providers may prescribe ACTIQ.
• Inform the patient that they must sign the Patient-Responder Agreement to acknowledge that they understand the risks of ACTIQ.
• Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program [see Warnings and Precautions (5.7)].
Medication Guide

ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

IMPORTANT:
Do not use ACTIQ unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant. Keep ACTIQ in a safe place away from children.

Get emergency medical help right away if:
• a child takes ACTIQ. ACTIQ can cause an overdose and death in any child who uses it.
• an adult who has not been prescribed ACTIQ uses it.
• an adult who is not already taking opioids around-the-clock uses ACTIQ.

These are medical emergencies that can cause death. If possible, remove ACTIQ from the mouth.

ACTIQ is:
• A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. ACTIQ is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use ACTIQ if you are not opioid tolerant.
• An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about ACTIQ:
• Get emergency help right away if you take too much ACTIQ (overdose). When you first start taking ACTIQ, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
• Taking ACTIQ with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
• Never give anyone else your ACTIQ. They could die from taking it. Selling or giving away ACTIQ is against the law.
• Store ACTIQ securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
• If you stop taking your around-the-clock opioid pain medicine for your cancer pain, you must stop using ACTIQ. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.

continued

• ACTIQ is available only through a program called the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access program. To receive ACTIQ, you must:
  ◦ talk to your healthcare provider
  ◦ understand the benefits and risks of ACTIQ
  ◦ agree to all of the instructions
  ◦ sign the Patient-Prescriber Agreement form
• ACTIQ is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your ACTIQ prescription filled.
• Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take ACTIQ if:
• You are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.
• You have severe asthma, trouble breathing, or other lung problems.
• You have a bowel blockage or have narrowing of the stomach or intestines.
• You are allergic to any of the ingredients in ACTIQ. See the end of this Medication Guide for a complete list of ingredients in ACTIQ.
• You have short-term pain that you would expect to go away in a few days, such as:
  ◦ pain after surgery
  ◦ headache or migraine
  ◦ dental pain

Before taking ACTIQ, tell your healthcare provider if you have a history of:
• troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
• head injury, seizures
• low blood pressure
• abuse of street or prescription drugs, alcohol addiction, or mental health problems
• diabetes. Each ACTIQ unit contains about ½ teaspoon (2 grams) of sugar.
• mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
• problems urinating
• liver, kidney, thyroid problems
• pancreas or gallbladder problems

Tell your healthcare provider if you are:
• Pregnant or planning to become pregnant. Prolonged use of ACTIQ during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
• Breastfeeding. ACTIQ passes into breast milk and may harm your baby.
• Taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking ACTIQ with certain other medicines can cause serious side effects that could lead to death.

When taking ACTIQ:
• Do not change your dose. Take ACTIQ exactly as prescribed by your healthcare provider.
• Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
• See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use ACTIQ.
• Finish the unit completely in 15 minutes to get the most relief. If you finish ACTIQ too quickly, you will swallow more of the medicine and get less relief.

continued
• Do not bite or chew. You will get less relief for your breakthrough cancer pain.
  • You may drink some water before using ACTIQ but you should not drink or eat anything while using ACTIQ.
  • You must not use more than 2 units of ACTIQ during each episode of breakthrough cancer pain:
    ◦ Use 1 unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
    ◦ If your breakthrough cancer pain is not relieved 15 minutes after you finished the ACTIQ unit, use only 1 more unit of ACTIQ at this time.
    ◦ If your breakthrough pain does not get better after the second unit of ACTIQ, call your healthcare provider for instructions.
  • Do not use another unit of ACTIQ at this time.
  • Wait at least 4 hours before treating a new episode of breakthrough cancer pain with ACTIQ.
  • It is important for you to keep taking your around-the-clock opioid pain medicine.
  • Talk to your healthcare provider if your dose of ACTIQ does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of ACTIQ needs to be changed.
  • Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
  • If you begin to feel dizzy, sick to your stomach, or very sleepy before ACTIQ is completely dissolved, remove ACTIQ from your mouth.
  • Do not stop taking ACTIQ without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
  • After you stop taking, or when ACTIQ is no longer needed, see “How should I dispose of ACTIQ units when they are no longer needed?” for proper disposal of ACTIQ.
  • Dispose of expired, unwanted, or unused ACTIQ by following the “How should I dispose of ACTIQ units when they are no longer needed?” sections of this Medication Guide below. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.
  • DO NOT Drive or operate heavy machinery, until you know how ACTIQ affects you. ACTIQ can make you sleepy, dizzy, or lightheaded.
  • DO NOT Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ACTIQ may cause you to overdose and die.
  • DO NOT Switch from ACTIQ to other medicines that contain fentanyl without talking to your healthcare provider. The amount of fentanyl in a dose of ACTIQ is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of ACTIQ that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of ACTIQ:
• constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, weakness, anxiety, depression, rash, trouble sleeping. Call your healthcare provider if you have any of these symptoms and they are severe.
• Decreased blood pressure. This can make you feel dizzy or light-headed if you get up too fast from sitting or lying down.
• ACTIQ contains sugar. Cavities and tooth decay can happen in people taking ACTIQ. When taking ACTIQ, you should talk to your dentist about proper care of your teeth.

Get emergency medical help if you have:
• trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
• These symptoms can be a sign that you have used too much ACTIQ or the dose is too high for you. These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more ACTIQ until you have talked to your healthcare provider.

These are not all the possible side effects of ACTIQ. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

How should I store ACTIQ?
• Always keep ACTIQ in a safe place away from children and from anyone for whom it has not been prescribed. Protect ACTIQ from theft.
  ◦ You can use the ACTIQ Child Safety Kit to help you store ACTIQ and your other medicines out of the reach of children. It is very important that you use the items in the ACTIQ Child Safety Kit to help protect the children in your home or visiting your home.
  ◦ If you were not offered a Child Safety Kit when you received your medicine, call 888-534-3119.
  ◦ The ACTIQ Child Safety Kit contains important information on the safe storage and handling of ACTIQ.
  ◦ The Child Safety Kit includes:
    • A child-resistant lock that you use to secure the storage space where you keep ACTIQ (See Figure 1).
    • A portable locking pouch for you to keep a small supply of ACTIQ nearby. The rest of your ACTIQ must be kept in a locked storage space.
      ◦ Keep this pouch secured with its lock and keep it out of the reach and sight of children (See Figure 2).
    • A child-resistant temporary storage bottle (See Figure 3).
• Store ACTIQ at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
• Do not freeze ACTIQ.
• Keep ACTIQ in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use ACTIQ.
• Keep ACTIQ dry.

How should I dispose of ACTIQ units when they are no longer needed?

Disposing of ACTIQ units after use:
Partially used ACTIQ units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed ACTIQ. You must properly dispose of the ACTIQ handle right away after use even if there is little or no medicine left on it. After you have finished the ACTIQ unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If any medicine remains on the used ACTIQ unit after you have finished:
• Place the used ACTIQ unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See Figure 4).

Temporary Storage of Used ACTIQ Units:
If you did not finish the entire ACTIQ unit and you cannot dissolve the medicine under hot running water right away, put the used ACTIQ unit in the temporary storage bottle that you received in the ACTIQ Child Safety Kit. Push the used ACTIQ unit into the opening on the top until it falls completely into the bottle. Never leave unused or partially used ACTIQ units where children or pets can get to them (See Figure 5).

Disposing of Used ACTIQ Units from the Temporary Storage Bottle:
You must dispose of all used ACTIQ units in the temporary storage bottle at least one time each day, as follows:
1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See Figure 6).

2. Remove one ACTIQ unit from the temporary storage bottle. Hold the ACTIQ by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.

4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each ACTIQ handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice. Do not flush entire unused ACTIQ units, ACTIQ handles, or blister packages down the toilet.

Disposing of unopened ACTIQ units: Dispose of any unopened ACTIQ units remaining from a prescription as soon as they are no longer needed, as follows:
1. Remove all ACTIQ from the locked storage space (See Figure 7).

2. Remove one ACTIQ unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See Figures 8A and 8B).

3. Hold ACTIQ by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See Figures 9A and 9B).

4. Throw the handle away in a place that is out of the reach of children (See Figure 10).

5. Repeat steps 1 through 4 for each ACTIQ unit.
6. Flush the toilet twice after the medicine ends from 5 ACTIQ units have been cut off (See Figure 11). Do not flush more than 5 ACTIQ units at a time.
Do not flush entire unused ACTIQ units, ACTIQ handles, or blister packages down the toilet. If you need help with disposal of ACTIQ, call Teva Pharmaceuticals at 1-888-483-8279, or call your local Drug Enforcement Agency (DEA) office.

**General information about ACTIQ**
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use ACTIQ only for the purpose for which it was prescribed. Do not give ACTIQ to other people, even if they have the same symptoms you have. ACTIQ can harm other people and even cause death. Sharing ACTIQ is against the law. This Medication Guide summarizes the most important information about ACTIQ. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about ACTIQ that is written for healthcare professionals. For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

**What are the ingredients of ACTIQ?**
**Active Ingredient:** fentanyl citrate
**Inactive Ingredients:** sugar, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch and confectioner’s sugar.

**Patient Instructions for Use**
Before you use ACTIQ, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use ACTIQ the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use ACTIQ.

**When you get an episode of breakthrough cancer pain, use the dose of ACTIQ prescribed by your healthcare provider as follows:**
- You may drink some water before using ACTIQ but you should not drink or eat anything while using ACTIQ.
- Each unit of ACTIQ is sealed in its own blister package (See Figure 12). Do not open the blister package until you are ready to use ACTIQ.

**Figure 12**

- When you are ready to use ACTIQ, cut open the package using scissors. Peel back the blister backing, and remove the ACTIQ unit (See Figures 13A and 13B). The end of the unit printed with “ACTIQ” and the strength number of the unit (“200”, “400”, “600”, “800”, “1200”, or “1600”) is the medicine end that is to be placed in your mouth. Hold the ACTIQ unit by the handle (See Figure 14).

**Figure 13A**

**Figure 13B**

**Figure 14**

1. Place the medicine end of the ACTIQ unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the ACTIQ unit around in your mouth, especially along the inside of your cheeks (See Figure 15).

3. Twirl the handle often.
4. Finish the ACTIQ unit completely over 15 minutes to get the most relief. If you finish ACTIQ too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew ACTIQ. You will get less relief for your breakthrough cancer pain.**
   - If you cannot finish all of the medicine on the ACTIQ unit and cannot dissolve the medicine under hot tap water right away, immediately put the ACTIQ unit in the temporary storage bottle for safe keeping (See Figure 16).
     - Push the ACTIQ unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the ACTIQ unit as soon as you can.

**Figure 15**

**Figure 16**

See “How should I dispose of ACTIQ units when they are no longer needed?” for proper disposal of ACTIQ.

Distributed by:
Teva Pharmaceuticals USA, Inc. call 1-888-483-8279
North Wales, PA 19454
Revised 10/2019
ACTIQ is a registered trademark of Cephalon, Inc. or its affiliates.
ACTMG-013
©2000-2019 Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. All rights reserved.
Printed in USA
This Medication Guide has been approved by the U.S. Food and Drug Administration.
ACT-40028