HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACTIQ safely and effectively. See full prescribing information for ACTIQ.

ACTIQ (fentanyl citrate) oral transmucosal lozenge, CII
Initial U.S. Approval: 1998

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

See full prescribing information for complete boxed warning.

- **Must not be used in opioid non-tolerant patients. (1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. (5.1)**
- **Contraindicated in management of acute or postoperative pain. (4)**
- **Contains medicine in an amount that can be fatal to a child. Keep out of reach of children and discard opened units properly. (5.2)**
- **Use with strong and moderate CYP450 3A4 inhibitors may result in potentially fatal respiratory depression. (7)**

----------INDICATIONS AND USAGE----------

ACTIQ is an opioid analgesic indicated only for management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. (1)

----------DOSAGE AND ADMINISTRATION----------

- Initial dose of ACTIQ: 200 mcg. Prescribe an initial supply of six 200 mcg ACTIQ units. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single ACTIQ dosage unit per breakthrough cancer pain episode. (1, 2)
- Limit consumption to four or fewer units per day once successful dose is found. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Solid drug matrix on a handle in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain. (4)
- Intolerance or hypersensitivity to fentanyl, ACTIQ, or its components. (4)

----------WARNINGS AND PRECAUTIONS----------

- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.1, 5.3)
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("ACTIQ Welcome Kit") (5.2, 17.4)
- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1, 5.3)
- Titrate ACTIQ cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to hypoventilation. (5.5, 5.7)
- Administer ACTIQ with extreme caution in patients susceptible to intracranial effects of CO_2 retention. (5.6)

----------ADVERSE REACTIONS----------

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

Dental decay has been reported. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Cephalon, Inc., at 1-800-896-5855 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Monitor patients who begin or end therapy with potent inhibitors of CYP450 3A4 for signs of opioid toxicity. (5.3, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Safety and efficacy below age 16 years have not been established. (8.4)
- Administer ACTIQ with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [02/2007]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

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

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

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. All units must be kept out of the reach of children and opened units properly discarded [*see Patient Counseling Information (17.5, 17.6), Contraindications (4) and How Supplied/Storage and Handling (16.2)*].

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

1 INDICATIONS AND USAGE

ACTIQ (oral transmucosal fentanyl citrate) is indicated only for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. For this reason, Actiq is contraindicated in the management of acute or postoperative pain.

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

2 DOSAGE AND ADMINISTRATION

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

2.1 Dose Titration

Starting Dose: Individually titrate ACTIQ to a dose that provides adequate analgesia and minimizes side effects. 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.

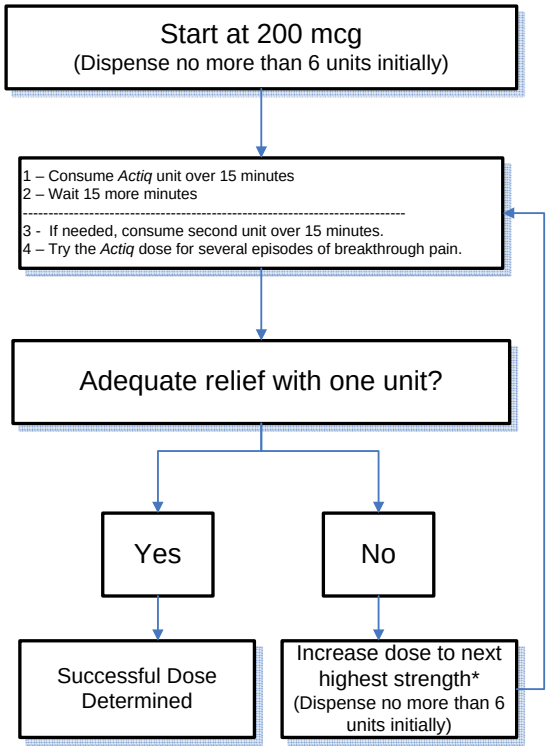
From this initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single ACTIQ dosage unit per breakthrough cancer pain episode. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased. Patients should record their use of ACTIQ over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: 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 and consuming units which individually may be subtherapeutic, 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. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

***Actiq* Titration Process**

See Boxed Warning



*** Available dosage strengths include: 200, 400, 600, 800, 1200, and 1600 mcg.**

2.2 Dosage Adjustment

Increase the dose of ACTIQ when patients require more than one dosage unit per breakthrough cancer pain episode for several consecutive episodes. When titrating to an appropriate dose, prescribe small quantities (six units) at each titration step. 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.

2.3 Administration of ACTIQ

Open the blister package 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 *[see Clinical Pharmacology (12.3)]*.

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.

2.4 Discontinuation of ACTIQ

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.

3 DOSAGE FORMS AND STRENGTHS

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 (16.3)]*.

4 CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of ACTIQ.

5 WARNINGS AND PRECAUTIONS

***See Boxed Warning* - WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE**

5.1 Hypoventilation (Respiratory Depression)

As with all opioids, there is a risk of clinically significant hypoventilation in patients using ACTIQ. Accordingly, follow all patients for symptoms of respiratory depression. Hypoventilation may occur more readily when opioids are given in conjunction with other agents that depress respiration.

5.2 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must 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 How Supplied/Storage and Handling, (16.1, 16.2), and Patient Counseling Information (17.1, 17.7)*].

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.

ACTIQ could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

5.3 Additive CNS Depressant Effects

The concomitant use of ACTIQ with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects *[see Drug Interactions (7)]*.

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of ACTIQ if warranted.

5.4 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking ACTIQ of these dangers and counsel them accordingly.

5.5 Chronic Pulmonary Disease

Because potent opioids can cause hypoventilation, titrate ACTIQ with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of ACTIQ may further decrease respiratory drive to the point of respiratory failure.

5.6 Head Injuries and Increased Intracranial Pressure

Administer ACTIQ with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.7 Cardiac Disease

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

5.8 MAO Inhibitors

ACTIQ is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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 adverse reactions seen with ACTIQ are typical opioid side effects. Frequently, these adverse reactions will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including ACTIQ are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

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 effect 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. Adverse reactions are included regardless of causality or severity.

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.

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. The goal of titration in these trials was to find the dose of ACTIQ that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 1 lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. 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)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=230)	800-1400 mcg (n=138)	1600 mcg (n=54)	>1600 mcg (n=41)	Any Dose* (n=254)
Body As A Whole					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	9	9	11	20	17
Confusion	1	6	2	0	4
Anxiety	3	0	2	0	3
Abnormal Gait	0	1	4	0	2
Dry Mouth	1	1	2	0	2
Nervousness	1	1	0	0	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

* 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 1% 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
Cardiovascular: Migraine
Digestive: Diarrhea, dyspepsia, flatulence
Metabolic and Nutritional: Peripheral edema, dehydration
Nervous: Hypesthesia
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: Flu syndrome, abscess, bone pain
Cardiovascular: Deep thrombophlebitis, hypertension, hypotension
Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis
Hemic 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: Alopecia, 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 and are commonly associated with opioid administration or are of particular clinical interest. 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)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=98)	800-1400 mcg (n=83)	1600 mcg (n=53)	>1600 mcg (n=27)	Any Dose* (n=152)
Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	9
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	36	25	26	45
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anxiety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confusion	2	5	13	7	10
Depression	9	4	2	7	9
Insomnia	5	1	8	4	7
Abnormal Gait	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	0	4	3
Stupor	4	1	0	0	3
Vasodilatation	1	1	4	0	3
Thinking Abnormal	2	1	0	0	2
Abnormal Dreams	1	1	0	0	1
Convulsion	0	1	2	0	1
Myoclonus	0	0	4	0	1
Tremor	0	1	2	0	1
Vertigo	0	0	4	0	1
Respiratory					
Dyspnea	15	16	8	7	22
Skin					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

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

The following reactions not reflected in Table 2 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain
Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder
Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage
Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia
Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia
Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder
Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder
Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased
Skin and Appendages: Skin ulcer, alopecia
Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion
Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

The following reactions occurred with a frequency of less than 1% in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity
Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia
Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder
Hemic and Lymphatic: Bleeding time increased
Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst
Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder
Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma
Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration
Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash
Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

6.2 Post-Marketing Experience

Adverse reactions are reported voluntarily from a population of uncertain size, and, therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to ACTIQ.

The following adverse reactions have been identified during postapproval use of ACTIQ (which contains approximately 2 grams of sugar per unit):

Digestive: Dental decay of varying severity including dental caries, tooth loss, and gum line erosion.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when ACTIQ is given concurrently with agents that affect CYP3A4 activity. The concomitant use of Actiq with strong CYP3A4 inhibitors (e.g, ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentsdrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving Actiq concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, thus should be avoided.

Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.

Concomitant use of ACTIQ with an MAO inhibitor, or within 14 days of discontinuation, is not recommended *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women. ACTIQ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

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.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for ACTIQ.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

Pregnant female New Zealand white rabbits were treated with fentanyl (0, 25, 100, 400 mcg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 400 mcg/kg (approximately 5-times the human dose of 1600 mcg every 6 hours on a mg/m^2 basis).

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore do not use ACTIQ during labor and delivery.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use ACTIQ in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ACTIQ.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 16 years 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) C_{max} and AUC_{0-8} 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 8.38 (192%; 0.84-50.78), respectively, for children ages ≥11 to <16 y (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 and older, while 15 (6%) were 75 years of age and 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 Renal or 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 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

8.7 Gender

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. ACTIQ may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of ACTIQ to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [*see How Supplied/Storage and Handling (16.1, 16.2)*].

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require

careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since ACTIQ may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Guide the administration of ACTIQ by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of ACTIQ overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation [*see Clinical Pharmacology (12.2)*].

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the ACTIQ unit, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of severe ACTIQ overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

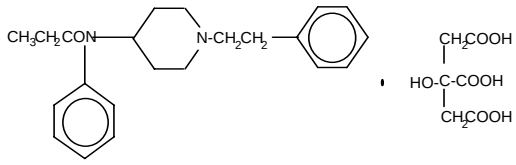
Although muscle rigidity interfering with respiration has not been seen following the use of ACTIQ, this is possible with fentanyl and other opioids. If it occurs, manage it by using assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

11 DESCRIPTION

ACTIQ (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, 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 at pH 7.4 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:



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 a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia

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. As a result, the dose of ACTIQ should be individually titrated to achieve the desired effect *[see Dosage and Administration (2)]*.

Central Nervous System

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 both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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).

Gastrointestinal System

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 is delayed in the small intestine 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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System

All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of ACTIQ. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication [*see Boxed Warning - Warnings: Importance Of Proper Patient Selection and Potential for Abuse, Contraindications (4), Warnings And Precautions (5.1), Adverse Reactions (6), and Overdosage (10)*].

12.3 Pharmacokinetics

Absorption

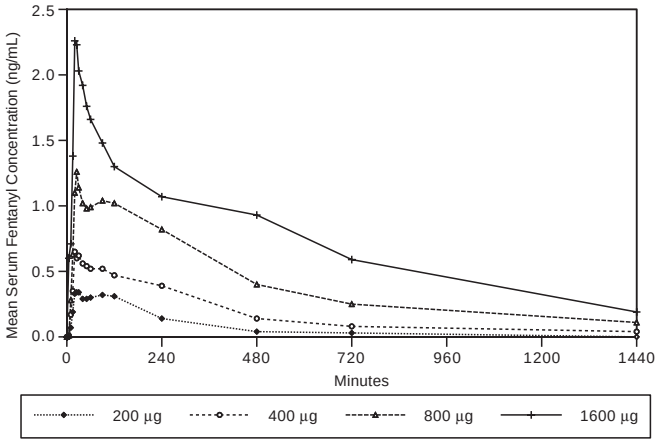
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of ACTIQ is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of ACTIQ, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

Dose proportionality among four of the available strengths of ACTIQ (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects (n=11). Mean serum fentanyl levels following these four doses of ACTIQ are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0\rightarrow\infty}$ increased in a dose-dependent manner that is approximately proportional to the ACTIQ administered.

Figure 1.
Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of ACTIQ



The pharmacokinetic parameters of the four strengths of ACTIQ tested in the dose-proportionality study are shown in Table 3. The mean C_{max} ranged from 0.39 - 2.51 ng/mL. The median time of maximum plasma concentration (T_{max}) across these four doses of ACTIQ varied from 20 - 40 minutes (range of 20 - 480 minutes) as measured after the start of administration.

Table 3.
Pharmacokinetic Parameters* in Adult Subjects Receiving 200, 400, 800, and 1600 mcg Units of ACTIQ

Pharmacokinetic Parameter	200 mcg	400 mcg	800mcg	1600 mcg
T_{max}, minute median (range)	40 (20-120)	25 (20-240)	25 (20-120)	20 (20-480)
C_{max}, ng/mL mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

* 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 acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism

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

Elimination

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. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

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.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 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 either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of ACTIQ to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200 and 1600 mcg). A "successful" dose was defined as a dose where one unit of ACTIQ could be used consistently 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 4.

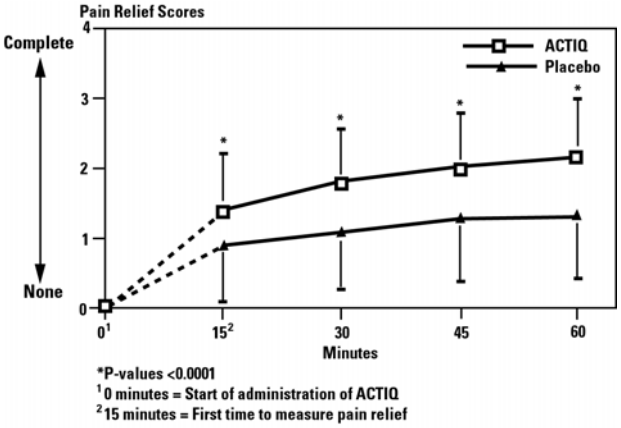
Table 4. Successful Dose of ACTIQ Following Initial Titration

ACTIQ Dose	Total No. (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean +/- SD	789 +/- 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 (Mean±SD) During the Double-Blind Phase - All Patients with Evaluable Episodes on Both ACTIQ and Placebo (N=86)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

ACTIQ is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in ACTIQ can be fatal to a child. Patients and their caregivers must be instructed to keep ACTIQ out of the reach of children [*see Boxed Warning - Warnings: Importance Of Proper Patient Selection and Potential For Abuse, Warnings And Precautions (5), and Patient Counseling Information (17.1)*].

Store at 20-25ºC (68-77ºF) 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.

16.2 Disposal of ACTIQ

Patients must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child resistant blister package, yet may contain enough medicine to be fatal to a child [*see Patient Counseling Information (17.5)*].

A temporary storage bottle is provided as part of the ACTIQ Welcome Kit [*see Patient Counseling Information (17.4)*]. This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the Medication Guide.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in *Patient Counseling Information (17.6)* and in the *Medication Guide (17.7)*. If additional assistance is required, call Cephalon, Inc. at 1-800-896-5855.

16.3 How Supplied

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. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

Dosage Strength (fentanyl base)	Carton/Blister Package Color	NDC Number
200 mcg	Gray	NDC 63459-502-30
400 mcg	Blue	NDC 63459-504-30
600 mcg	Orange	NDC 63459-506-30
800 mcg	Purple	NDC 63459-508-30
1200 mcg	Green	NDC 63459-512-30
1600 mcg	Burgundy	NDC 63459-516-30

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

17 PATIENT COUNSELING INFORMATION

See the *Medication Guide (17.7)* for specific patient instructions.

17.1 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that ACTIQ contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. 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 How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.2), and Patient Counseling Information (17.4)*].

17.2 Dental Care

Because each ACTIQ unit contains approximately 2 grams of sugar (hydrated dextrates), frequent consumption may increase the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking ACTIQ [*see Adverse Reactions (6.2)*]. In some of these patients, dental decay occurred despite reported routine oral hygiene. As dental decay in cancer patients may be multi-factorial, patients using ACTIQ should consult their dentist to ensure appropriate oral hygiene.

17.3 Diabetic Patients

Advise diabetic patients that ACTIQ contains approximately 2 grams of sugar per unit.

17.4 ACTIQ Welcome Kit

Provide patients and their caregivers with an ACTIQ Welcome Kit, which contains educational materials and safe interim storage containers to help patients store ACTIQ and other medicines out of the reach of children. Patients and their caregivers should also have an opportunity to watch the patient safety video, which provides proper product use, storage, handling and disposal directions. Patients should also have an opportunity to discuss the video with their health care providers. To obtain a supply of welcome kits or videos for patient viewing, health care professionals can call Cephalon, Inc. at 1-800-896-5855.

17.5 Disposal of Used ACTIQ Units

Patients must be instructed to dispose of completely used and partially used ACTIQ units.

1) 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.

2) 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.

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.

17.6 Disposal of Unopened ACTIQ Units When No Longer 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:

1) Remove the ACTIQ unit from its blister package using scissors, and hold the ACTIQ by its handle over the toilet bowl.

2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.

3) Dispose of the handle in a place that is out of the reach of children.

4) 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 [*see How Supplied/Storage and Handling (16.1)*].

Detailed instructions for the 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.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for Cephalon, Inc. (1-800-896-5855) or seek assistance from their local DEA office.

17.7 Medication Guide

Medication Guide
Actiq® (AK-tik) CII
(oral transmucosal fentanyl citrate)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

WARNING: You MUST keep *Actiq* in a safe place out of the reach of children. Accidental ingestion by a child is a medical emergency and can result in death. **If a child accidentally takes *Actiq*, get emergency help right away.**

Read the Medication Guide that comes with *Actiq* before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Share this important information with members of your household.

What is the most important information I should know about *Actiq*?

1. ***Actiq* can cause life threatening breathing problems which can lead to death:**
   - **if it is used by anyone who is not already taking other opioid pain medicines and their body is not used to these medicines (not opioid tolerant)**
   - **if it is not used exactly as prescribed.**
2. **Your doctor will prescribe a starting dose of *Actiq* that is different than other fentanyl containing medicines you may have been taking. Do not substitute *Actiq* for other fentanyl medicines without talking with your doctor.**

What is *Actiq*?

- *Actiq* is a prescription medicine that contains the medicine fentanyl. ***Actiq* is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.**

***Actiq* is to be used only to treat breakthrough pain in adult patients with cancer (16 years of age and older) who are already taking other opioid pain medicines for their constant (around-the-clock) cancer pain.** *Actiq* is started only after you have been taking other opioid pain medicines and your body has gotten used to them (you are opioid tolerant). **Do not use *Actiq* if you are not opioid tolerant.**

- You must stay under your doctor's care while taking *Actiq*.

- ***Actiq* must not be used for short-term pain from injuries and surgery.**

- **Prevent theft and misuse. Keep *Actiq* in a safe** place to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs. **Never give *Actiq* to anyone else**, even if they have the same symptoms you have. It may harm them and even cause death. **Selling or giving away this medicine is against the law.**

Who should not take *Actiq*?

Do Not Take *Actiq* if you:

- are not already taking other opioid pain medicines for your constant (around-the-clock) cancer pain. **Never use *Actiq* for short-term pain from injuries or surgery** or pain that will go away in a few days, such as pain from doctor or dentist visits, or any short-lasting pain.

- **are allergic to anything in *Actiq*.** The active ingredient in *Actiq* is fentanyl. See the end of this Medication Guide for a complete list of ingredients in *Actiq*.

What should I tell my doctor before I start taking *Actiq*?

Tell your doctor about all of your medical and mental problems, especially the ones listed below:

- Trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- A head injury or brain problem
- Liver or kidney problems
- Seizures (convulsions or fits)
- Slow heart rate or other heart problems
- Low blood pressure
- Mental problems including major depression or hallucinations (seeing or hearing things that are not there)
- A past or present drinking problem or alcoholism, or a family history of this problem
- A past or present drug abuse or addiction problem, or a family history of this problem
- If you are diabetic. Each *Actiq* unit contains about ½ teaspoon (2 grams) of sugar.

Tell your doctor if you are:

- **pregnant or planning to become pregnant.** *Actiq* may harm your unborn baby.

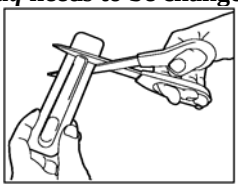
- **breast feeding.** Fentanyl passes through your breast milk and it can cause serious harm to your baby. **You should not use *Actiq* while breast feeding.**

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with *Actiq*. Sometimes, the doses of certain medicines and *Actiq* need to be changed if used together. **Do not take any medicine while using *Actiq* until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using *Actiq*. Be especially careful about other medicines that make you sleepy such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.**

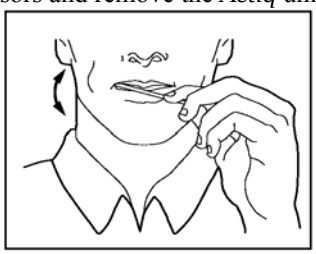
Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

How should I use *Actiq*?

- Use *Actiq* exactly as prescribed. Do not take *Actiq* more often than prescribed. **Talk to your doctor about your pain. Your doctor can decide if your dose of *Actiq* needs to be changed.**



- Each unit of *Actiq* is sealed in its own blister package.
- **Do not open the blister package until you are ready to use *Actiq*.**
- When you are ready to use *Actiq*, cut open the package using scissors and remove the *Actiq* unit.



- Place *Actiq* in your mouth between your cheeks and gums and actively suck on the medicine.
- Move *Actiq* around in your mouth, especially along your cheeks.
- Twirl the handle often.
- Finish the *Actiq* 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.
- **Do not bite or chew *Actiq*. You will get less relief for your breakthrough pain.**
- You may drink some water before using *Actiq* but you should not drink or eat anything while using *Actiq*.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before *Actiq* is completely dissolved, remove *Actiq* from your mouth. Dispose of *Actiq* right away or put it in the temporary storage bottle in the Welcome Kit for later disposal.

If you have more than 4 episodes of breakthrough cancer pain per day, talk to your doctor. The dose of *Actiq* may need to be adjusted.

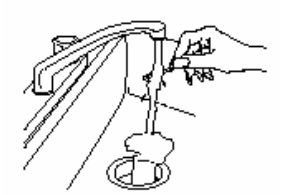
- **If you take too much *Actiq* or overdose, call 911 or your local emergency number for help.**

How should I dispose of *Actiq* 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.** Please follow these directions to dispose of the handle:

1. Once 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.

2. If any medicine remains on the handle after you have finished, place the handle under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets.



3. If you did not finish the entire *Actiq* unit and you cannot dissolve the medicine under hot running water right away, put the *Actiq* in the temporary storage bottle that you received in the *Actiq* Welcome Kit for safe keeping. Push the *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.**
4. Dispose of the handles in the temporary storage bottle as soon as you can by following the directions in steps 1 and 2. You must dispose of all handles in the temporary storage bottle at least once a day.

Do not flush entire unused *Actiq* units, *Actiq* handles, or blister packages down the toilet.

What should I avoid while taking *Actiq*?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how *Actiq* affects how alert you are. *Actiq* can make you sleepy. Ask your doctor when it is okay to do these activities.

- **Do not drink alcohol while using *Actiq*.** It can increase your chance of getting dangerous side effects.

- **Do not take any medicine while using *Actiq* until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using *Actiq*. Be especially careful about medicines that make you sleepy such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.**

What are the possible or reasonably likely side effects of *Actiq*?

- ***Actiq* can cause serious breathing problems that can become life-threatening, especially if used the wrong way**. See "What is the most important information I should know about *Actiq*?"

- **Call your doctor or get emergency medical help right away if you:**
  - **have trouble breathing**
  - **have extreme drowsiness with slowed breathing**
  - **have slow shallow breathing (little chest movement with breathing)**
  - **feel faint, very dizzy, confused, or have unusual symptoms**

These can be symptoms that you have taken too much (overdose) *Actiq* or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- ***Actiq* can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.

- ***Actiq* can cause physical dependence.** Do not stop taking *Actiq* or any other opioid without talking to your doctor. 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.

- **There is a chance of abuse or addiction with *Actiq*.** The chance is higher if you are or have been addicted to or abused other medications, street drugs, or alcohol, or if you have a history of mental problems.

The most common side effects of *Actiq* are nausea, vomiting, dizziness and sleepiness. Other side effects include headache, low energy and constipation. Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including *Actiq* and is unlikely to go away without treatment. Talk to your doctor about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking *Actiq*.

Actiq contains sugar. Cavities and tooth decay have occurred in patients taking *Actiq*. When taking *Actiq*, you should talk to your dentist about proper care of your teeth.

Talk to your doctor about any side effects that bother you or that do not go away.

These are not all the possible side effects of *Actiq*. For a complete list, ask your doctor.

How should I store *Actiq*?

- **Keep *Actiq* in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes *Actiq*, get emergency help right away.**
- ***Actiq* is supplied in single sealed child-resistant blister packages.** Store *Actiq* at room temperature, 59° to 86°F (15° to 30°C) until ready to use.
- **Always keep *Actiq* in a secure place to protect from theft.**

How should I dispose of unopened *Actiq* units when they are no longer needed?

- Dispose of any unopened *Actiq* units remaining from a prescription as soon as they are no longer needed.
- If you are no longer using *Actiq* or if you have unused *Actiq* in your home, please follow these steps to dispose of the *Actiq* as soon as possible.

1. Remove all *Actiq* from the locked storage space.
2. Remove one *Actiq* unit from its blister package using scissors, and 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 steps 2, 3, and 4 for each *Actiq*.
6. Flush the toilet twice after 5 *Actiq* units have been cut. 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 Cephalon Professional Services at 1-800-896-5855.

General Information About the Safe and Effective Use of *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 doctor. You can also ask your pharmacist or doctor for information about *Actiq* that is written for healthcare professionals. You can also call Cephalon, Inc. at 1-800-896-5855.

What are the ingredients of *Actiq*?

Active Ingredient: fentanyl citrate

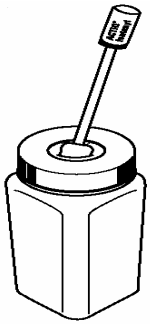
Inactive Ingredients: Sugar, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

How do I use the *Actiq* Welcome Kit?

- You can use the *Actiq* Welcome 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* Welcome Kit to protect the children in your home.
- If you were not offered a Welcome Kit when you received your medicine, call Cephalon Professional Services at 1-800-896-5855 to request one.

The *Actiq* Welcome Kit contains:

- **A child-resistant lock** for you to secure the storage space where you keep *Actiq* and any other medicines at home.
- **A portable locking pouch** for you to keep a small supply of *Actiq* nearby for your immediate use. The rest of your *Actiq* must be kept in the locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children.



- A **child-resistant temporary storage bottle.**
- If for some reason you cannot finish the entire *Actiq* unit and cannot immediately dissolve the medicine under hot tap water, immediately put the *Actiq* unit in the temporary storage bottle for safe keeping.
  - 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.
- See "How should I dispose of unopened *Actiq* units when they are no longer needed?" for proper disposal of *Actiq*.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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