ACTIQ® CII

(oral transmucosal fentanyl citrate)

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

***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, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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.

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.

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 all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

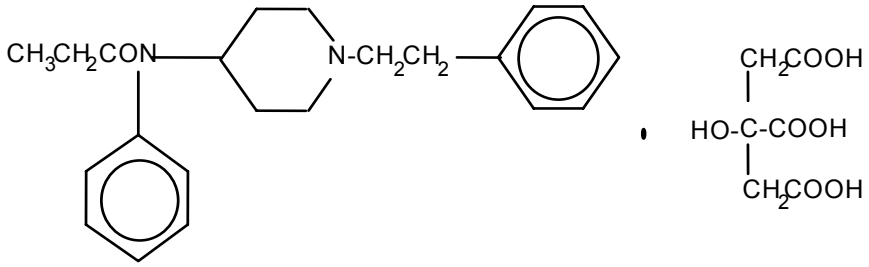
WARNING: May be habit forming

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 radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner 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:



Actiq is available in six strengths equivalent to 200, 400, 600, 800, 1200, or 1600 mcg fentanyl base that is identified by the text on the solid drug matrix, the dosage unit handle tag, the blister package, and the shelf carton.

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid mu-receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacologic effects of the interaction of fentanyl with mu-receptors are analgesia and sedation.

Other opioid effects may include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria and confusion or difficulty in concentrating at clinically relevant doses.

Clinical Pharmacology

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 opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to 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**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

Opioids increase the tone and decrease contractions of the smooth muscle of the gastrointestinal (GI) tract. This results in prolongation in GI transit time and may be responsible for the constipating effect of opioids. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others, difficulty in urination.

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*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

Serious or fatal respiratory depression can occur, even at recommended doses, in vulnerable individuals. As with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals.

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* 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 BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.)

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.

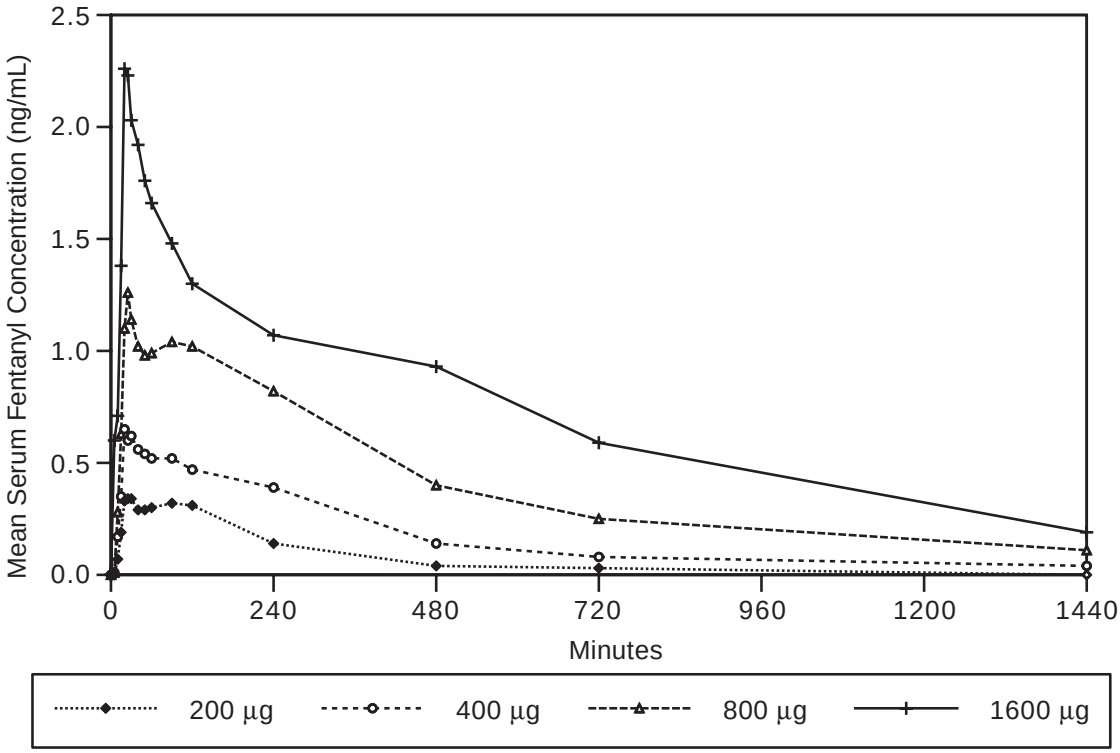
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

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. 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 1. 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 1.
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)

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 **PRECAUTIONS: Drug Interactions** for additional information).

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 *OTFC* administration is about 7 hours.

Special Populations:

Elderly Patients:

Elderly patients have been shown to be twice as sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. While a formal study evaluating the safety profile of *Actiq* in the elderly population has not been performed, in the 257 opioid tolerant cancer patients studied with *Actiq*, approximately 20% were over age 65 years. No difference was noted in the safety profile in this group compared to those aged less than 65 years, though they did titrate to lower doses than younger patients (see **PRECAUTIONS**).

Patients with Renal or Hepatic Impairment:

Actiq should be administered with caution to patients with liver or kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs and effects on plasma-binding proteins (see **PRECAUTIONS**).

Although fentanyl kinetics are known to be altered in both hepatic and renal disease due to alterations in metabolic clearance and plasma proteins, individualized doses of *Actiq* have been used successfully for breakthrough cancer pain in patients with hepatic and renal disorders. The duration of effect for the initial dose of fentanyl is determined by redistribution of the drug, such that diminished metabolic clearance may only become significant with repeated dosing or with excessively large single doses. For these reasons, while doses titrated to clinical effect are recommended for all patients, special care should be taken in patients with severe hepatic or renal disease.

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 events.

CLINICAL TRIALS

Breakthrough Cancer Pain:

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). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. 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.

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 2.

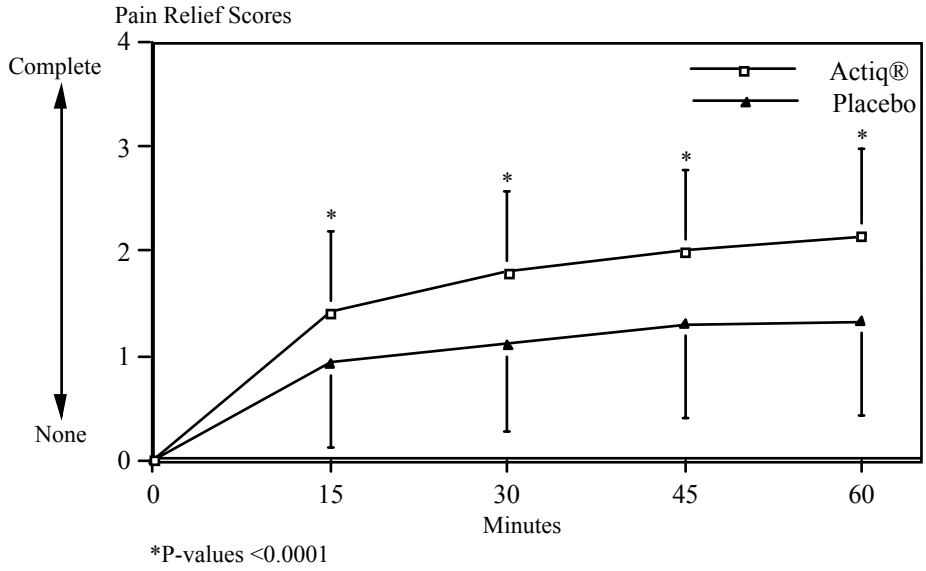
Table 2.
Successful Dose of *Actiq*
Following Initial Titration

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 produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration (see Figure 2).

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)



In this same study patients also rated the performance of medication to treat their breakthrough cancer pain using a different scale ranging from "poor" to "excellent." On average, placebo was rated "fair" and *Actiq* was rated "good."

INDICATIONS AND USAGE
(See BOX WARNING and CONTRAINDICATIONS)
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, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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.

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.

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. 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 (see **DOSAGE AND ADMINISTRATION**).

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount that can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly in a secured container.

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. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). 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, 50 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.

WARNINGS
See BOX WARNING
The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors), and alcoholic beverages may produce increased depressant effects. Hypoventilation, hypotension, and profound sedation may occur.

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.

Pediatric Use: The appropriate dosing and safety of *Actiq* in opioid tolerant children with breakthrough cancer pain have not been established below the age of 16 years.

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 **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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.

PRECAUTIONS
General
The initial dose of *Actiq* to treat episodes of breakthrough cancer pain should be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

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). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

The use of concomitant CNS active drugs requires special patient care and observation. (See **WARNINGS**.)

Hypoventilation (Respiratory Depression)
As with all opioids, there is a risk of clinically significant hypoventilation in patients using *Actiq*. Accordingly, all patients should be followed for symptoms of respiratory depression. Hypoventilation may occur more readily when opioids are given in conjunction with other agents that depress respiration.

Chronic Pulmonary Disease
Because potent opioids can cause hypoventilation, *Actiq* should be titrated 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.

Head Injuries and Increased Intracranial Pressure
Actiq should only be administered 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.

Cardiac Disease
Intravenous fentanyl may produce bradycardia. Therefore, *Actiq* should be used with caution in patients with bradyarrhythmias.

Hepatic or Renal Disease
Actiq should be administered with caution to patients with liver or kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs and effects on plasma binding proteins (see **PHARMACOKINETICS**).

Information for Patients and Their Caregivers
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 **SAFETY AND HANDLING, WARNINGS**, and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]. 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** – Post-Marketing Experience). In some of these patients, dental decay occurred despite reported oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

Diabetic patients should be advised that *Actiq* contains approximately 2 grams of sugar per unit.

Patients and their caregivers should be provided with an *Actiq* Welcome Kit, which contains educational materials and safe 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. Health care professionals should call 1-800-896-5855 to obtain a supply of welcome kits or videos for patient viewing.

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) Handles in the child-resistant container should be disposed of (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 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. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given 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, they should be instructed to call the toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

Laboratory Tests
The effects of *Actiq* on laboratory tests have not been evaluated.

Drug Interactions
See **WARNINGS.**

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450 3A4 isoform. Drugs that inhibit P450 3A4 activity may increase the bioavailability of swallowed fentanyl (by decreasing intestinal and hepatic first pass metabolism) and may decrease the systemic clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Drugs that induce cytochrome P450 3A4 activity may have the opposite effects. However, no *in vitro* or *in vivo* studies have been performed to assess the impact of those potential interactions on the administration of *Actiq*. Thus patients who begin or end therapy with potent inhibitors of CYP450 3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole and itraconazole), and protease inhibitors (e.g., ritanovir) while receiving *Actiq* should be monitored for a change in opioid effects and, if warranted, the dose of *Actiq* should be adjusted.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Because animal carcinogenicity studies have not been conducted with fentanyl citrate, the potential carcinogenic effect of *Actiq* is unknown.

Standard mutagenicity testing of fentanyl citrate has been conducted. There was no evidence of mutagenicity in the Ames *Salmonella* or *Escherichia* mutagenicity assay, the *in-vitro* mouse lymphoma mutagenesis assay, and the *in-vivo* micronucleus cytogenetic assay in the mouse.

Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dose group (1.25 mg/kg subcutaneously) in which one of twenty animals became pregnant.

Pregnancy - Category C
Fentanyl has been shown to impair fertility and to have an embryocidal effect with an increase in resorptions in rats when given for a period of 12 to 21 days in doses of 30 mcg/kg IV or 160 mcg/kg subcutaneously.

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. 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.

Labor and Delivery
Actiq is not indicated for use in labor and delivery.

Nursing Mothers
Fentanyl is excreted in human milk; therefore *Actiq* should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants.

Pediatric Use
See WARNINGS.

Geriatric Use
Of the 257 patients in clinical studies of *Actiq* in breakthrough cancer pain, 61 (24%) were 65 and over, while 15 (6%) were 75 and over.

Those patients over the age of 65 titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients. Previous studies with intravenous fentanyl showed that elderly patients are twice as sensitive to the effects of fentanyl as the younger population.

No difference was noted in the safety profile of the group over 65 as compared to younger patients in *Actiq* clinical trials. However, greater sensitivity in older individuals cannot be ruled out. Therefore, caution should be exercised in individually titrating *Actiq* in elderly patients to provide adequate efficacy while minimizing risk.

ADVERSE REACTIONS
Pre-Marketing Clinical Trial 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 events seen with *Actiq* are typical opioid side effects. Frequently, these adverse events will cease or decrease in intensity with continued use of *Actiq*, as the patient is titrated to the proper dose. Opioid side effects should be expected and managed accordingly.

The most serious adverse effects associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. All patients should be followed 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 events are included regardless of causality or severity.

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 3 lists by dose groups, adverse events 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 events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.
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	200-600 mcg	800-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	230	138	54	41	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

The following adverse events not reflected in Table 3 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 events 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 4 lists by dose groups, adverse events 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 events are listed in descending order of frequency within each body system.

Table 4.

PERCENT OF PATIENTS WITH ADVERSE EVENTS COMMONLY ASSOCIATED WITH OPIOID ADMINISTRATION OR OF PARTICULAR CLINICAL INTEREST WHICH OCCURRED DURING LONGTERM TREATMENT (EVENTS IN 1% OR MORE OF PATIENTS)

Dose Group	200-600 mcg	800-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	98	83	53	27	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

The following events not reflected in Table 4 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 events 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

Post-Marketing Experience
The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, 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*.
Digestive: Dental decay of varying severity including dental caries, tooth loss, and gum line erosion.

DRUG ABUSE AND DEPENDENCE
Fentanyl is a mu-opioid agonist and a Schedule II controlled substance that can produce drug dependence of the morphine type. *Actiq* may be subject to misuse, abuse and addiction.

The administration of *Actiq* should be guided 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.

The handling of *Actiq* should be managed 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 **SAFETY AND HANDLING**).

OVERDOSAGE
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**).

General
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.

Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person
Ventilatory support should be provided, intravenous access obtained, and naloxone or other opioid antagonists should be employed 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.

Treatment of Overdose in Opioid-Tolerant Patients
Ventilatory support should be provided and intravenous access obtained 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.

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, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well controlled.

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, it should be managed by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

DOSAGE AND ADMINISTRATION
***Actiq* is contraindicated in non-opioid tolerant individuals.**

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects (see **Dose Titration**).

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.

Physicians and dispensing pharmacists must specifically question patients and caregivers about the presence of children in the home on a full time or visiting basis and counsel accordingly regarding the dangers to children of inadvertent exposure to *Actiq*.

Administration of *Actiq*
The blister package should be opened 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.

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, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

Patients and caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. While all units should be disposed of immediately after use, partially used units represent a special risk and must be disposed of as soon as they are consumed and/or no longer needed. Patients and caregivers should be advised to dispose of any units remaining from a prescription as soon as they are no longer needed (see **Disposal Instructions**).

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 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, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

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.

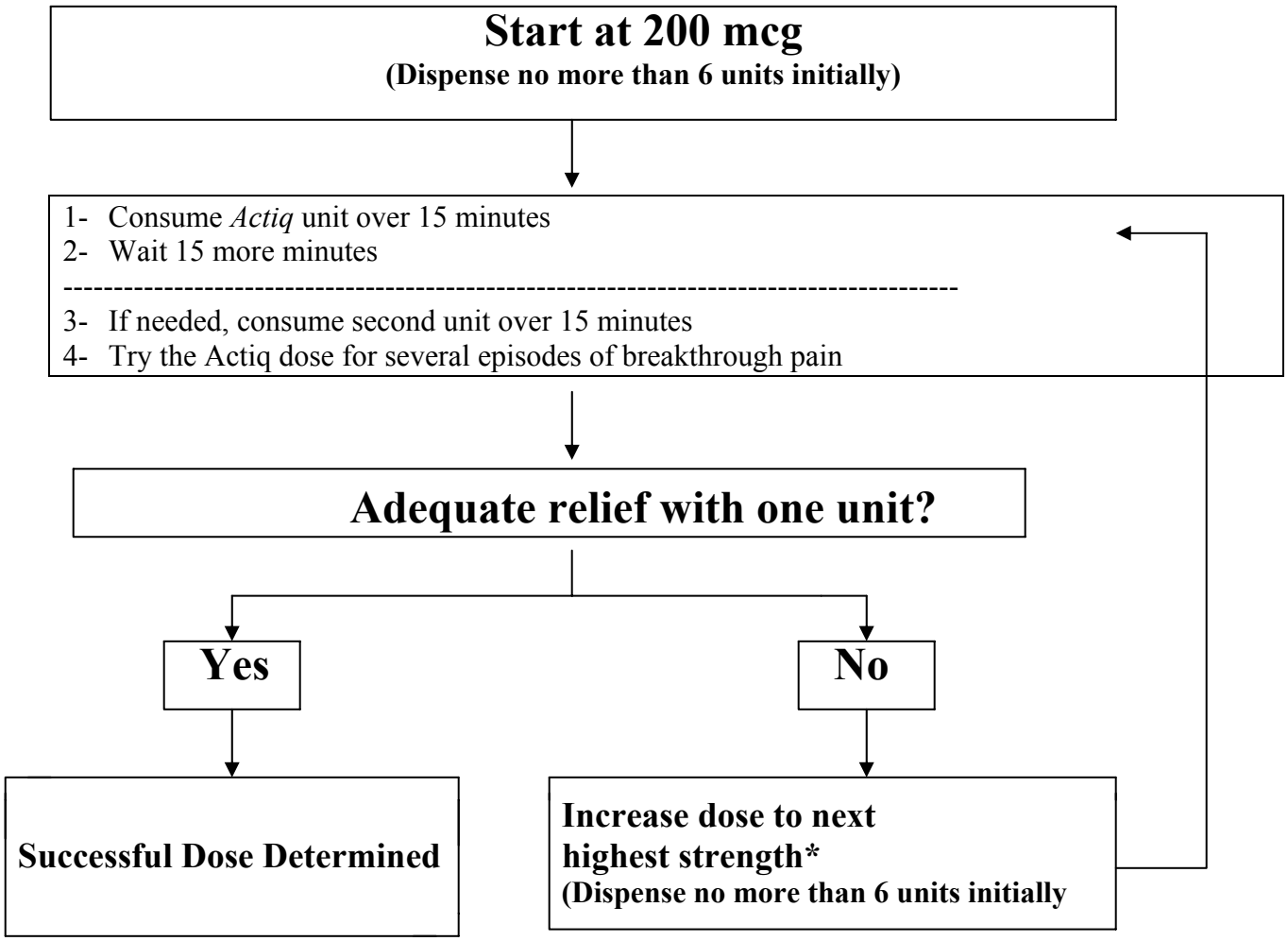
Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients 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, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated 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.

Daily Limit: 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. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.

Actiq Titration Process

See Box Warning



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

Dosage Adjustment

Experience in a long-term study of *Actiq* used in the treatment of breakthrough cancer pain suggests that dosage adjustment of both *Actiq* and the maintenance (around-the-clock) opioid analgesic may be required in some patients to continue to provide adequate relief of breakthrough cancer pain.

Generally, the *Actiq* dose should be increased when patients require more than one dosage unit per breakthrough cancer pain episode for several consecutive episodes. When titrating to an appropriate dose, small quantities (six units) should be prescribed at each titration step. Physicians should consider increasing the around-the-clock opioid dose used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

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.

SAFETY 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 **BOX WARNING, WARNINGS, PRECAUTIONS,** and **PATIENT LEAFLET**).

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.) *Actiq* should be protected from freezing and moisture. Do not use if the blister package has been opened.

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 **Information for Patients**).

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). 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 patient leaflet.

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 **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

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.

Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed.

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.

Rx only.

DEA order form required. A Schedule CII narcotic.

Manufactured by:
Cephalon, Inc., Salt Lake City, UT 84116

U. S. Patent No. 4,671,953
Printed in USA

Label code XXX Date

[redacted]

Patient Leaflet

Cephalon

Actiq® C_{II}

(ORAL TRANSMUCOSAL FENTANYL CITRATE)

WARNING: Keep out of the reach of children

Read this information carefully before using ***Actiq***. If you have any questions after reading this patient leaflet, talk to your doctor.

Actiq* contains medicine that could be harmful or fatal to a child. You MUST keep *Actiq* out of the reach of children.** Explain to children that ***Actiq is a medicine for your use only.

Actiq* can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines on a regular schedule to relieve chronic cancer pain.** If you have not been taking these types of medicines, do not use ***Actiq because it may cause your breathing to slow down to a dangerous level or even to stop. Some examples of opioid pain medicines are Duragesic®, Dilaudid®, methadone, morphine, MS Contin®, and OxyContin®.

Actiq* must only be used for breakthrough cancer pain.** Do not use ***Actiq if you have pain that will go away in a few days, such as pain from surgery, from doctor or dentist visits, or any other short-lasting pain.

Do not let anyone else use *Actiq*. It is for your use only.

If someone accidentally takes *Actiq*:
If the person is not awake and alert, call 911 or call for emergency help immediately.
If the person is awake and alert, call Poison Control at 1-800-690-3924.

WARNING: MAY BE HABIT FORMING

WARNING: Keep out of the reach of children

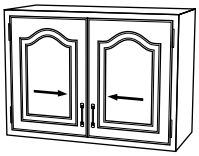
Important Information For People Who Have Children In The Home: You MUST keep ***Actiq*** out of the reach of children. ***Actiq*** contains medicine that could be harmful or fatal to a child. Please pay close attention to the child warnings in this patient leaflet.

How to use the *Actiq* Welcome Kit

You have been prescribed an ***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.

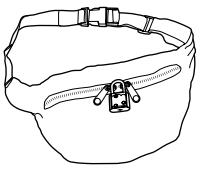
Child-resistant lock

After you have chosen a storage space for ***Actiq*** and your other medicines, secure this space with the child-resistant lock included in the Welcome Kit.



Portable locking pouch

YOU MAY KEEP A SMALL SUPPLY OF ***ACTIQ*** IN THE PORTABLE LOCKING POUCH SO THAT IT IS 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.



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*** 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 to dispose of ***Actiq*** after use).

IF YOU DID NOT RECEIVE AN *ACTIQ* WELCOME KIT, PLEASE CALL 1-800-896-5855.

How to store *Actiq* in your home

- ***ACTIQ*** AND YOUR OTHER MEDICINES MUST BE STORED IN A LOCKED STORAGE SPACE. BE SURE TO USE THE CHILD-RESISTANT LOCK THAT YOU RECEIVED IN THE WELCOME KIT.
- ALWAYS KEEP ***ACTIQ*** IN ITS BLISTER PACKAGE UNTIL YOU ARE READY TO USE IT. DO NOT USE ***ACTIQ*** IF THE BLISTER PACKAGE HAS BEEN DAMAGED OR OPENED BEFORE YOU ARE READY TO USE IT.
- STORE ***ACTIQ*** AT CONTROLLED ROOM TEMPERATURE 68 TO 77°F (20-25°C). DO NOT REFRIGERATE OR FREEZE. DO NOT STORE ***ACTIQ*** ABOVE 77°F (25°C). REMEMBER, THE INSIDE OF YOUR CAR CAN GET HOT IN THE SUMMER.

What is *Actiq*?

ACTIQ CONTAINS A PRESCRIPTION OPIOID (NARCOTIC) PAIN-RELIEVING MEDICINE CALLED FENTANYL. WHEN YOU PLACE ***ACTIQ*** IN YOUR MOUTH, IT SLOWLY DISSOLVES AND THE MEDICINE IS ABSORBED THROUGH THE LINING OF YOUR MOUTH. FROM YOUR MOUTH, IT GOES INTO YOUR BLOODSTREAM, WHERE IT WORKS TO RELIEVE YOUR BREAKTHROUGH CANCER PAIN.

When to use *Actiq*

Actiq is used to relieve the flares called breakthrough cancer pain, that your regularly prescribed pain medicine does not control. ***Actiq*** should be taken along with your regularly prescribed cancer pain medicine. **Do not stop taking your regularly prescribed pain medicine.**

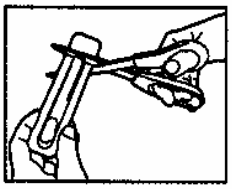
When not to use *Actiq*

- You should **not** use ***Actiq*** if you are having short-term pain, including pain from injuries and surgery.
- YOU SHOULD **NOT** USE ***ACTIQ*** UNLESS YOU HAVE BREAKTHROUGH CANCER PAIN AND HAVE BEEN TAKING A PRESCRIPTION OPIOID (NARCOTIC) PAIN MEDICINE EVERY DAY ON A REGULAR SCHEDULE.

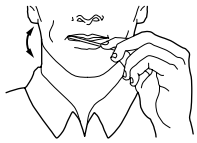
How to use *Actiq*

WHEN YOU FIRST START USING ***ACTIQ***, YOUR DOCTOR WILL HELP YOU FIND THE DOSE OF ***ACTIQ*** THAT WILL RELIEVE YOUR PAIN. USE ***ACTIQ*** EXACTLY AS YOUR DOCTOR OR NURSE TOLD YOU TO USE IT. YOUR DOCTOR WILL TELL YOU HOW OFTEN YOU CAN TAKE ***ACTIQ*** SAFELY.

STEP 1. EACH ***ACTIQ*** UNIT IS SEALED IN ITS OWN BLISTER PACKAGE. **DO NOT OPEN THE 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.



STEP 2. 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.



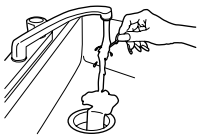
FINISH THE ***ACTIQ*** COMPLETELY IN 15 MINUTES TO GET THE MOST RELIEF. IF YOU FINISH ***ACTIQ*** TOO QUICKLY, YOU WILL SWALLOW MORE OF THE MEDICINE AND GET LESS RELIEF.

IF FOR SOME REASON YOU ARE NOT FINISHING THE ENTIRE UNIT EACH TIME YOU HAVE AN EPISODE OF BREAKTHROUGH CANCER PAIN, YOU SHOULD CALL YOUR DOCTOR OR NURSE.
Do not bite or chew *Actiq*. You will get less relief of your breakthrough cancer pain.
IF YOU BEGIN TO FEEL DIZZY OR SICK TO YOUR STOMACH BEFORE YOU HAVE FINISHED THE MEDICINE, REMOVE ***ACTIQ*** FROM YOUR MOUTH. EITHER DISPOSE OF ***ACTIQ*** IMMEDIATELY OR PUT IT IN THE TEMPORARY STORAGE BOTTLE FOR LATER DISPOSAL.
YOU MAY DRINK SOME WATER BEFORE USING ***ACTIQ***, BUT YOU SHOULD NOT DRINK OR EAT ANYTHING WHILE USING ***ACTIQ***.

How to 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 immediately and properly dispose of the *Actiq* handle 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 immediately dissolve the medicine under hot running water, 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 partly 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 to expect from *Actiq*

You should begin to feel some relief while you are taking ***Actiq***. You may not get full relief for up to 45 minutes after you have finished taking ***Actiq***. If you do not get enough pain relief from just one ***Actiq***, your doctor may allow you to use another one. Do not use a second ***Actiq*** unless your doctor or nurse tells you that you may do so.
Some people will have side effects with ***Actiq***. The most common side effects are feeling sleepy, sick to your stomach, or dizzy. If you begin to feel very sleepy, remove the ***Actiq*** from your mouth or call another person in your household to help you.
FOR BEST RESULTS, LET YOUR DOCTOR OR NURSE KNOW ABOUT YOUR PAIN AND HOW ***ACTIQ*** IS WORKING FOR YOU SO THE DOSE CAN BE CHANGED, IF NEEDED.

Important safety information for patients and caregivers

YOU AND THE OTHER PEOPLE IN YOUR HOME SHOULD BE AWARE OF SOME IMPORTANT INFORMATION ABOUT ***ACTIQ***. **ALWAYS FEEL FREE TO CONTACT YOUR DOCTOR OR NURSE WITH ANY QUESTIONS OR CONCERNS YOU MAY HAVE ABOUT *ACTIQ* AND ANY SIDE EFFECTS.**

- A serious side effect of ***Actiq*** is slow, shallow breathing. This can occur if your dose of ***Actiq*** is too high or if you take too much ***Actiq***. You and your caregivers should discuss this side effect with your doctor. **Attention Caregivers:** If you see that the person taking ***Actiq*** has slow breathing or if you have a hard time waking the person up, remove the ***Actiq*** from their mouth and call for emergency help. (See What to do if a child or an adult accidentally takes ***Actiq***.)

- ***Actiq*** may change the effect of other medicines (prescription and over-the-counter). ***Actiq*** will also add to the effects of alcohol and medicines that make you sleepy (like sleeping pills, anxiety medicines, antihistamines, or tranquilizers). Make sure that you talk to your doctor before drinking alcohol or taking any medicines (other than your regularly scheduled opioid [narcotic] pain medicines) while using ***Actiq***.
- ***Actiq*** may cause some people to become sleepy, dizzy, or less alert. Discuss this with your doctor to get advice on whether it is safe for you to drive or operate machinery. Until you have experienced how this medicine affects you, do not drive a car or operate potentially dangerous machinery. You should discuss this further with your doctor.

- FREQUENT USE OF PRODUCTS THAT CONTAIN SUGAR MAY INCREASE THE RISK OF DENTAL CAVITIES OR TOOTH DECAY (EACH ***ACTIQ*** UNIT CONTAINS ABOUT ½ TEASPOON OF SUGAR). THE OCCURRENCE OF DRY MOUTH ASSOCIATED WITH THE USE OF OPIOID MEDICATIONS MAY ADD TO THIS RISK (***ACTIQ*** CONTAINS THE OPIOID MEDICATION FENTANYL). YOU SHOULD CONSULT YOUR DENTIST TO ENSURE APPROPRIATE DENTAL CARE WHILE USING ***ACTIQ***.
- DIABETIC PATIENTS SHOULD INFORM THEIR PHYSICIAN THAT THEY ARE TAKING ***ACTIQ***, WHICH CONTAINS TWO GRAMS OF SUGAR PER UNIT (APPROXIMATELY ½ TEASPOON).
- DO NOT USE ***ACTIQ*** IF YOU ARE PREGNANT OR NURSING UNLESS TOLD THAT YOU MAY DO SO BY YOUR DOCTOR.

What to do if a child or an adult accidentally takes *Actiq*

Actiq contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed ***Actiq***. In these people, ***Actiq*** can cause their breathing to slow down or even stop. If you think someone has accidentally taken ***Actiq***, follow these steps immediately:

1. REMOVE THE ***ACTIQ*** UNIT FROM THE PERSON'S MOUTH.
2. If the person is asleep, keep them awake by calling their name and shaking their arm or shoulder.
3. **If the person is <u>not awake</u> and alert, call 911 or call for emergency help.** If the person is awake and alert, call Poison Control at 1-800-690-3924.

While waiting for emergency help:

4. IF THE PERSON SEEMS TO BE BREATHING SLOWLY, EVERY 5 TO 10 SECONDS TELL THEM TO BREATHE.
5. IF THE PERSON HAS STOPPED BREATHING, GIVE MOUTH-TO-MOUTH RESUSCITATION UNTIL EMERGENCY HELP ARRIVES.

How to know if someone has accidentally taken *Actiq*

If someone has accidentally taken ***Actiq***, they may have these symptoms:

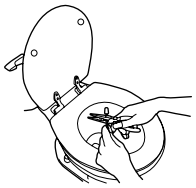
- Very sleepy
- Itching, especially around the nose and eyes
- Dizzy
- Sick to their stomach or vomiting
- Not breathing or breathing very slowly

When to call your doctor or nurse

- IF YOU HAVE SIDE EFFECTS THAT BOTHER YOU AND DO NOT GO AWAY.
- IF YOU WANT TO TAKE ANY OVER-THE-COUNTER MEDICINES.
- IF ANOTHER DOCTOR HAS PRESCRIBED ANY NEW MEDICINES FOR YOU.
- IF YOU DO NOT GET ENOUGH BREAKTHROUGH CANCER PAIN RELIEF.
- IF YOU ARE USING ***ACTIQ*** MORE THAN FOUR TIMES A DAY.
- IF YOU ARE NOT FINISHING THE ENTIRE ***ACTIQ*** UNIT.

When *Actiq* is 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:
Step 1. Remove all ***Actiq*** from the locked storage space.
STEP 2. REMOVE ONE ***ACTIQ*** UNIT FROM ITS BLISTER PACKAGE USING SCISSORS, AND HOLD THE ***ACTIQ*** BY ITS HANDLE OVER THE TOILET BOWL.
Step 3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.



Step 4. Throw the handle away in a place that is out of the reach of children.
Step 5. Repeat steps 2, 3, and 4 for each ***Actiq***. 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 1-800-896-5855. IF YOU STILL NEED HELP, CALL YOUR LOCAL DRUG ENFORCEMENT ADMINISTRATION (DEA) OFFICE.

WARNING: Keep out of the reach of children

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