ACTIQ® CII

(oral transmucosal fentanyl citrate)

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

***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.

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).

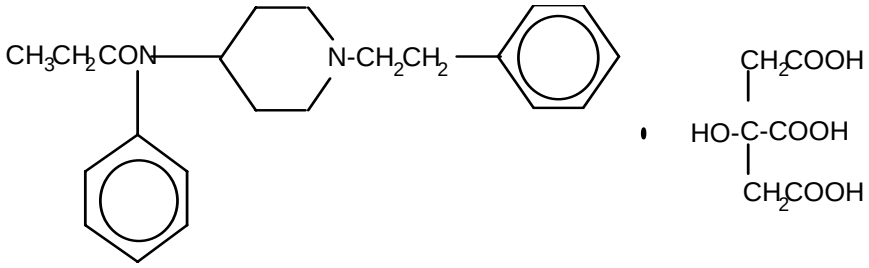
DESCRIPTION

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 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, and edible glue (modified food starch and confectioner's sugar).

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:
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. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, and analgesia. Like all pure opioid agonists 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.

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 lower doses than those usually required for analgesia.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic (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.

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 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. 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.

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 BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation).

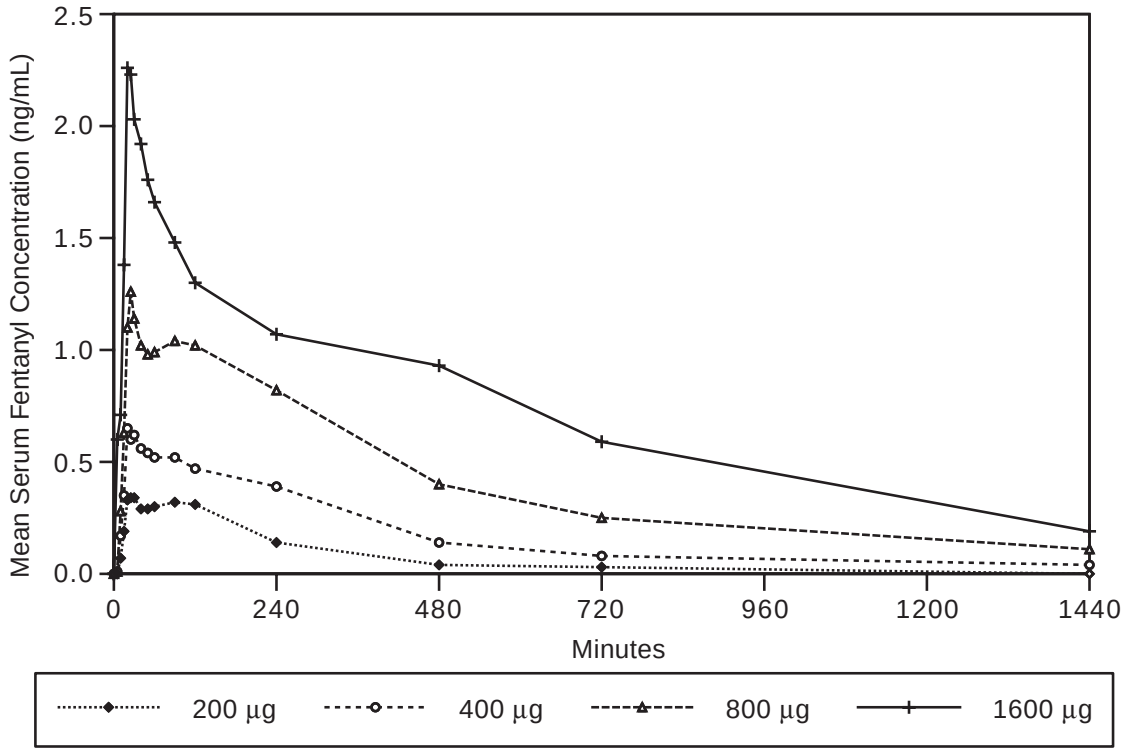
Pharmacokinetics
Absorption:
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability 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)**

* 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 **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.

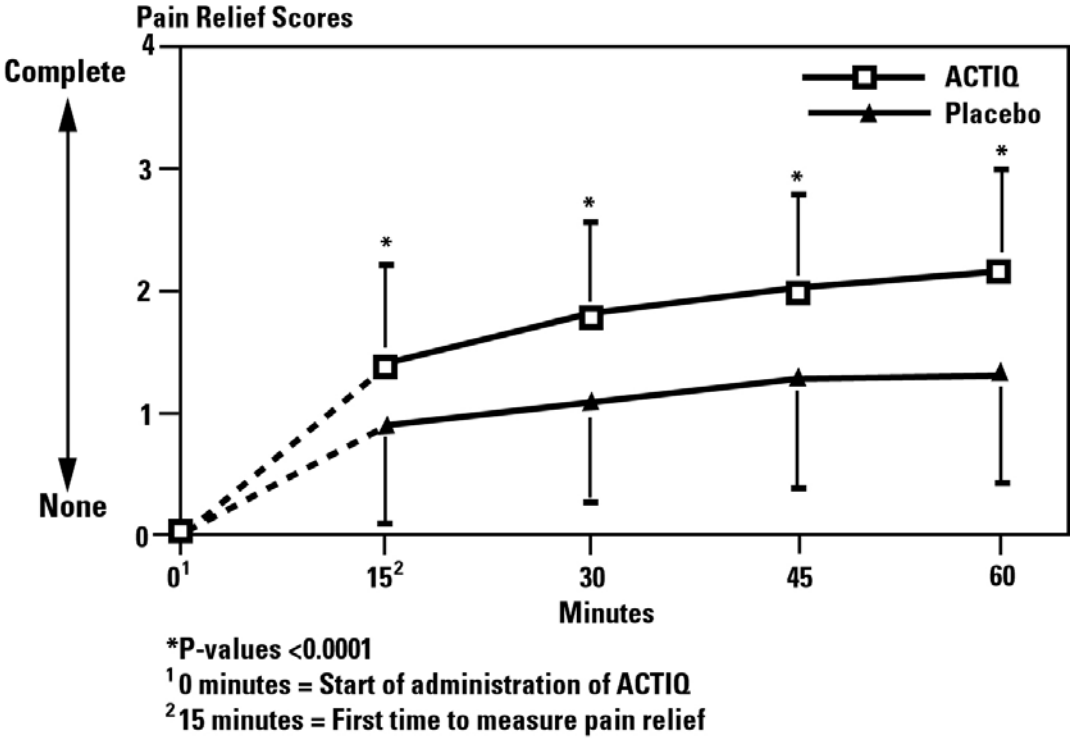
Table 2.
Successful Dose of ACTIQ
Following Initial Titration

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 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)



INDICATIONS AND USAGE
(See BOXED 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, 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.

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. 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.

WARNINGS
See BOXED 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 **MEDICATION GUIDE** 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 **MEDICATION GUIDE** 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. As dental decay in cancer patients may be multi-factorial, 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 Medication Guide. 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
No carcinogenicity studies have been conducted in animals with fentanyl citrate.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay 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.

Pregnancy - Category C
No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Fentanyl has been shown to increase resorptions in rats when given during organogenesis on gestation days 12 through 21 at IV doses of 30 mcg/kg or subcutaneous doses of 160 mcg/kg.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 3-times the human dose of 1600 mcg every 6 hours on a mg/m^2 basis). In contrast, the intravenous administration of fentanyl (0, 10, or 30 mcg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 30 mcg/kg/day group. There was no clear evidence of teratogenicity noted.

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).

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 years of age and older, while 15 (6%) were 75 years of age and older.

Those patients over the age of 65 years 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 years of age 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	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 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 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 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

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 the ACTIQ formulations that contained approximately 2 grams of sugar per unit:
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.

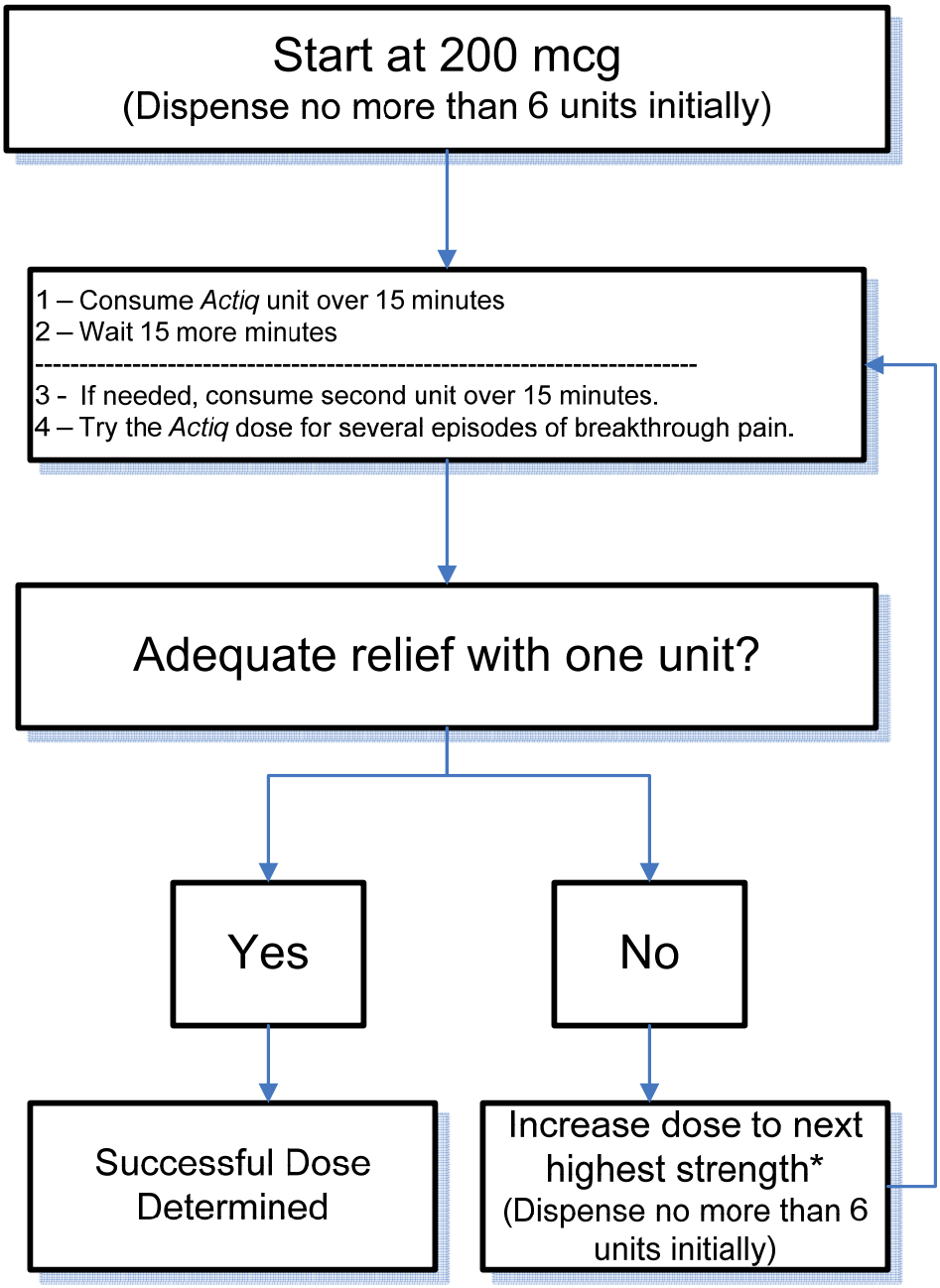
Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional ACTIQ unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are 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 Boxed 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 **BOXED WARNING, WARNINGS, PRECAUTIONS,** and **MEDICATION GUIDE**).

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 and Their Caregivers**).

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 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 **Information for Patients and Their Caregivers** and in the Medication Guide. 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.

℞ only.

DEA order form required. A Schedule CII narcotic.

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

Printed in USA

Label Code: XXXXX

Revised July 2006

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Oral Transmucosal Fentanyl Citrate (OTFC) CII

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

Oral Transmucosal Fentanyl Citrate (OTFC) contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. OTFC can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OTFC 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.

OTFC is indicated only for the management of breakthrough cancer pain in patients with malignancies who are <u>already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.</u> 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.

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

OTFC 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 OTFC 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).

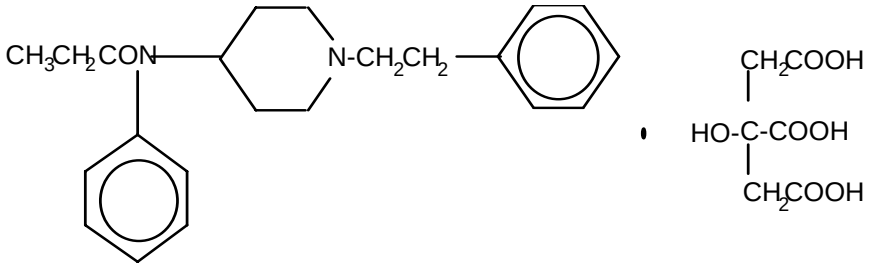
DESCRIPTION

Oral Transmucosal Fentanyl Citrate (OTFC) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. OTFC 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.

OTFC is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the OTFC 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:



OTFC 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, and edible glue (modified food starch and confectioner's sugar).

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:
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. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, and analgesia. Like all pure opioid agonists 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.

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 lower doses than those usually required for analgesia.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomic (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.

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 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 OTFC 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 OTFC. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of OTFC administration and may persist for several hours.

Serious or fatal respiratory depression can occur, even at recommended doses, in vulnerable individuals.

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

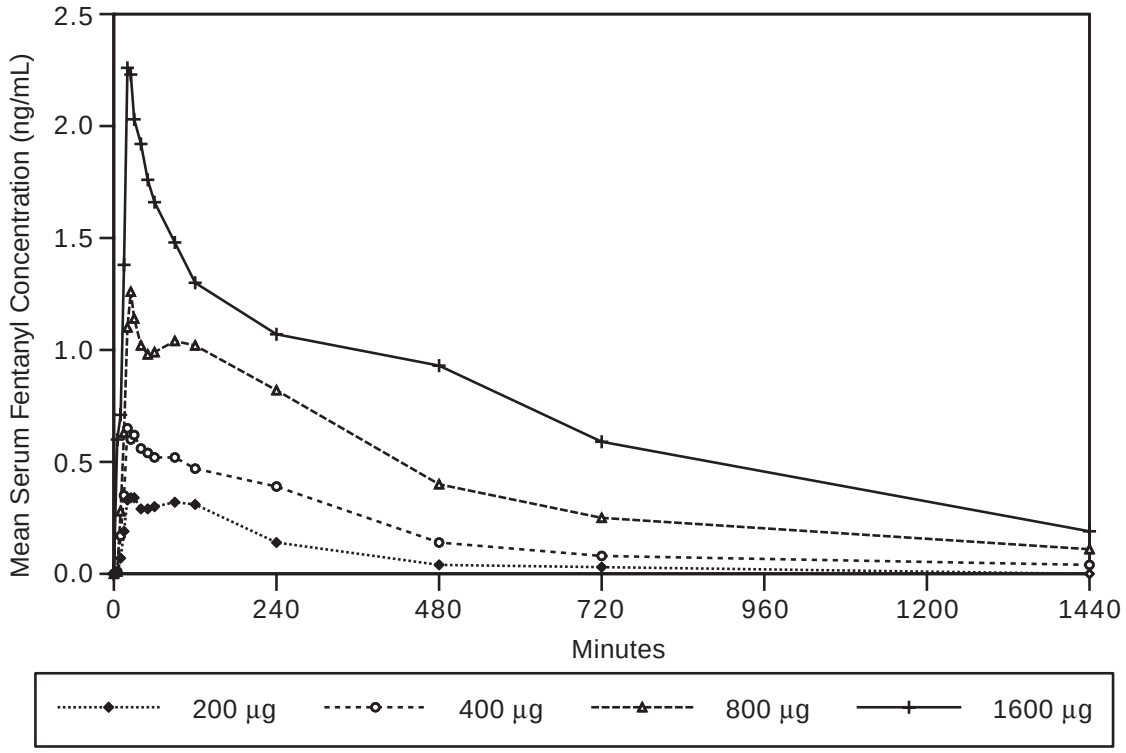
Pharmacokinetics
Absorption:
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability 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 Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of OTFC, 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 OTFC (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 OTFC 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 OTFC administered.

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



The pharmacokinetic parameters of the four strengths of OTFC 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 OTFC 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 OTFC

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 **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 OTFC in the elderly population has not been performed, in the 257 opioid tolerant cancer patients studied with OTFC, 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:
OTFC 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 OTFC 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:
Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC 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 OTFC could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

The successful dose of OTFC 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 OTFC 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.

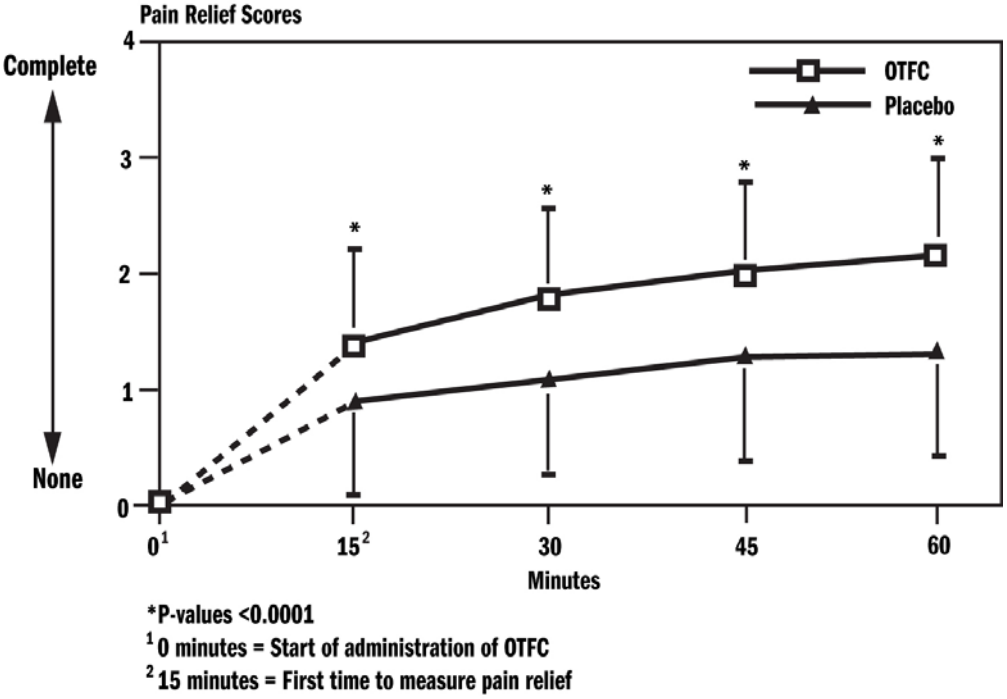
Table 2.
Successful Dose of OTFC
Following Initial Titration

OTFC 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.

OTFC 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 OTFC and Placebo (N=86)



INDICATIONS AND USAGE
(See BOXED WARNING and CONTRAINDICATIONS)
Oral Transmucosal Fentanyl Citrate (OTFC) 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.

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, OTFC is contraindicated in the management of acute or postoperative pain.

OTFC 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.

OTFC 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 OTFC 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, Oral Transmucosal Fentnayl Citrate (OTFC) 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.

OTFC is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

WARNINGS
See BOXED 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.

Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC 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 OTFC 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 **MEDICATION GUIDE** 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 Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC 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 OTFC. 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, OTFC 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 OTFC may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure
OTFC 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, OTFC should be used with caution in patients with bradyarrhythmias.

Hepatic or Renal Disease
OTFC 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 Oral Transmucosal Fentanyl Citrate (OTFC) 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 **MEDICATION GUIDE** for specific patient instructions).

Frequent consumption of sugar-containing products may increase the risk of dental decay (each OTFC 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 OTFC (see **ADVERSE REACTIONS** – Post-Marketing Experience). 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 OTFC should consult their dentist to ensure appropriate oral hygiene.
Diabetic patients should be advised that OTFC contains approximately 2 grams of sugar per unit.

Patients and their caregivers should be provided with an OTFC Welcome Kit, which contains educational materials and safe storage containers to help patients store OTFC 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 OTFC Units
Patients must be instructed to dispose of completely used and partially used OTFC 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 OTFC unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened OTFC 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 OTFC units:

1) Remove the OTFC unit from its blister package using scissors, and hold the OTFC 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 OTFC unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire OTFC units, OTFC 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 OTFC are provided in the OTFC Medication Guide. 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 OTFC 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 OTFC. 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 OTFC should be monitored for a change in opioid effects and, if warranted, the dose of OTFC should be adjusted.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No carcinogenicity studies have been conducted in animals with fentanyl citrate.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay 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.

Pregnancy - Category C
No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Fentanyl has been shown to increase resorptions in rats when given during organogenesis on gestation days 12 through 21 at IV doses of 30 mcg/kg or subcutaneous doses of 160 mcg/kg.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 3-times the

human dose of 1600 mcg every 6 hours on a mg/m^2 basis). In contrast, the intravenous administration of fentanyl (0, 10, or 30 mcg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 30 mcg/kg/day group. There was no clear evidence of teratogenicity noted.

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).

There are no adequate and well-controlled studies in pregnant women. OTFC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers
Fentanyl is excreted in human milk; therefore OTFC 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 OTFC 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 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 years of age as compared to younger patients in OTFC clinical trials. However, greater sensitivity in older individuals cannot be ruled out. Therefore, caution should be exercised in individually titrating OTFC in elderly patients to provide adequate efficacy while minimizing risk.

ADVERSE REACTIONS
Pre-Marketing Clinical Trial Experience
The safety of Oral Transmucosal Fentanyl Citrate (OTFC) has been evaluated in 257 opioid tolerant chronic cancer pain patients. The duration of OTFC 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 OTFC are typical opioid side effects. Frequently, these adverse events will cease or decrease in intensity with continued use of OTFC, 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 OTFC 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 OTFC 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 OTFC 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 OTFC 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	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 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 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 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
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 OTFC.

The following adverse reactions have been identified during post-approval use of the Actiq® formulations that contained approximately 2 grams of sugar per unit:
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. Oral Transmucosal Fentanyl Citrate (OTFC) may be subject to misuse, abuse and addiction.

The administration of OTFC 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 OTFC 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 Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC 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 OTFC 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 OTFC, 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
Oral Transmucosal Fentanyl Citrate (OTFC) is contraindicated in non-opioid tolerant individuals.

OTFC 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 OTFC.

Administration of OTFC
The blister package should be opened with scissors immediately prior to product use. The patient should place the OTFC 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 OTFC unit should be sucked, not chewed. A unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The OTFC unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in OTFC 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 OTFC 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 OTFC to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg OTFC 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 OTFC dosage unit per breakthrough cancer pain episode.

Patients should record their use of OTFC 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 OTFC 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 OTFC per episode, an increase in dose to the next higher available strength should be considered. At each new dose of OTFC during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of OTFC 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.

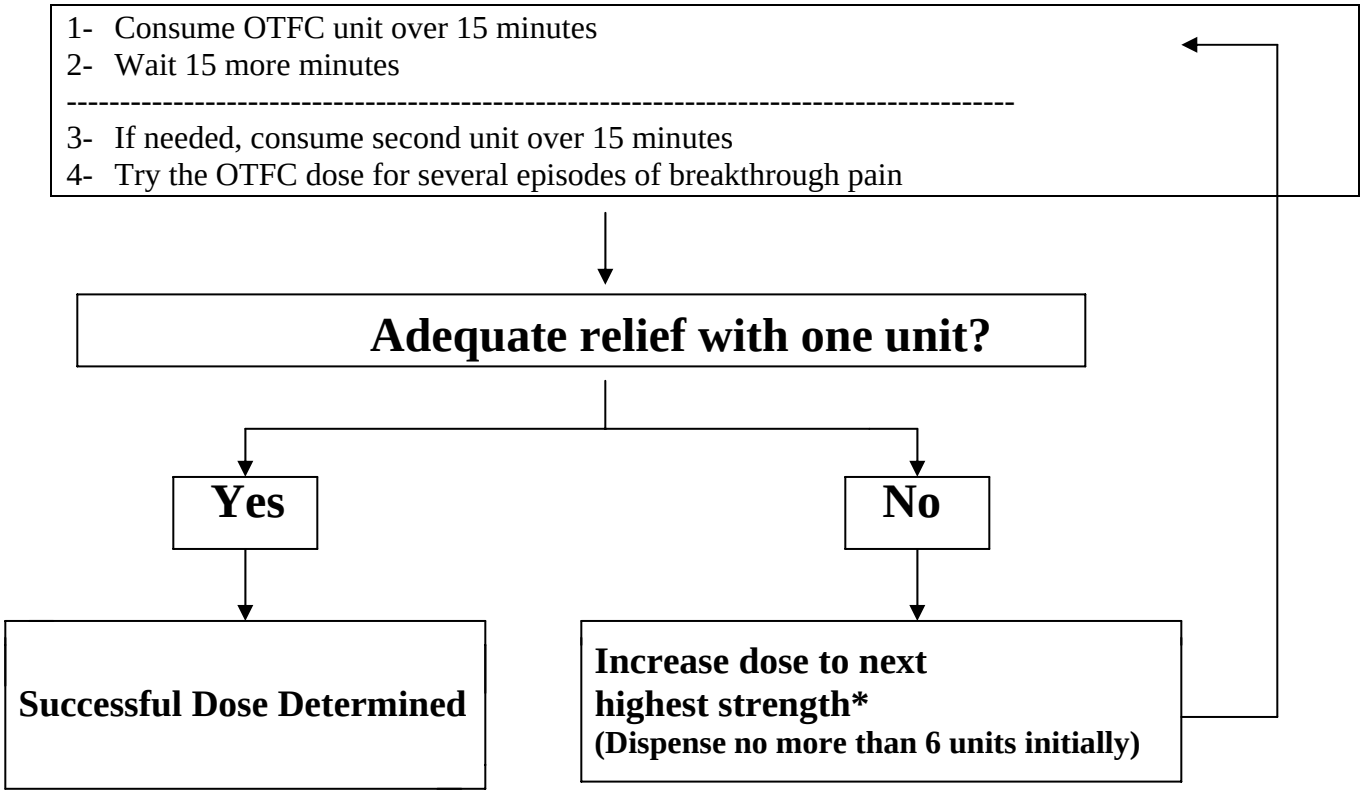
OTFC Titration Process

See BOXED WARNING

Start at 200 mcg

(Dispense no more than 6 units initially)

↓



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

Dosage Adjustment

Experience in a long-term study of OTFC used in the treatment of breakthrough cancer pain suggests that dosage adjustment of both OTFC 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 OTFC 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 OTFC

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

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in OTFC can be fatal to a child. Patients and their caregivers must be instructed to keep OTFC out of the reach of children (see **BOXED WARNING, WARNINGS, PRECAUTIONS,** and **MEDICATION GUIDE**).

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

DISPOSAL OF OTFC

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 and Their Caregivers**).

A temporary storage bottle is provided as part of the Oral Transmucosal Fentanyl Citrate (OTFC) 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 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 **Information for Patients and Their Caregivers** and in the Medication Guide. If additional assistance is required, referral to the OTFC 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC units. At each new dose of OTFC 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 55253-070-30
400 mcg	Blue	NDC 55253-071-30
600 mcg	Orange	NDC 55253-072-30
800 mcg	Purple	NDC 55253-073-30
1200 mcg	Green	NDC 55253-074-30
1600 mcg	Burgundy	NDC 55253-075-30

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:
Anesta Corp., Salt Lake City, UT 84116, USA

Label code: 074000112.01

Revised July, 2006

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 <u>exactly</u> 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

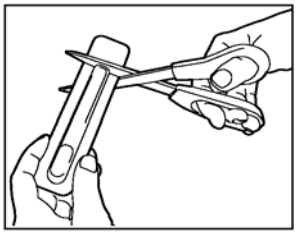
- **breast feeding.** Fentanyl passes through your breast milk and it can cause serious harm to your baby. **You should not use *Actiq* while breast feeding.**

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.**

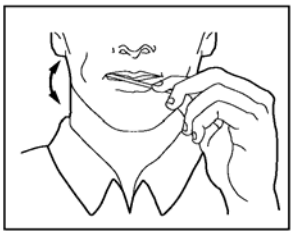
Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

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.

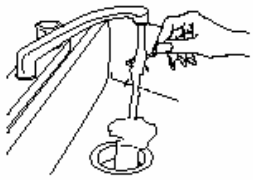
- **If you take too much *Actiq* or overdose, call 911 or your local emergency number for help.**

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.

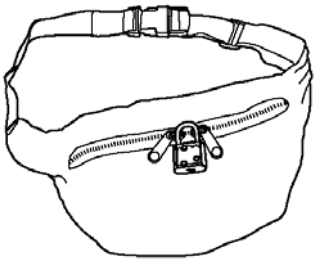
What are the ingredients of *Actiq*?

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

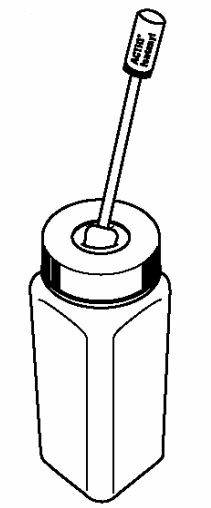
How do I use the *Actiq* Welcome Kit?

- 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 *Acti*q.

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

Rx Only.

Cephalon, Inc.
FRAZER, PA 19355, USA

Reference Number XXX

August, 2006

Medication Guide
Oral Transmucosal Fentanyl Citrate (OTFC) CII
(oral transmucosal fentanyl citrate)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

WARNING: You MUST keep Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC, get emergency help right away.**

Read the Medication Guide that comes with Oral Transmucosal Fentanyl Citrate (OTFC) 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 Oral Transmucosal Fentanyl Citrate (OTFC)?

3. **OTFC 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 <u>exactly</u> as prescribed.**
4. **Your doctor will prescribe a starting dose of OTFC that is different than other fentanyl containing medicines you may have been taking. Do not substitute OTFC for other fentanyl medicines without talking with your doctor.**

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl. **OTFC 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.**

OTFC 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. OTFC 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 OTFC if you are not opioid tolerant.**

- You must stay under your doctor's care while taking OTFC.
- **OTFC must not be used for short-term pain from injuries and surgery.**
- **Prevent theft and misuse. Keep OTFC 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 OTFC 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 Oral Transmucosal Fentanyl Citrate (OTFC)?

Do Not Take OTFC if you:

- are not already taking other opioid pain medicines for your constant (around-the-clock) cancer pain. **Never use OTFC 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 OTFC**. The active ingredient in OTFC is fentanyl. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my doctor before I start taking Oral Transmucosal Fentanyl Citrate (OTFC)?

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 OTFC unit contains about ½ teaspoon (2 grams) of sugar.

Tell your doctor if you are:

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

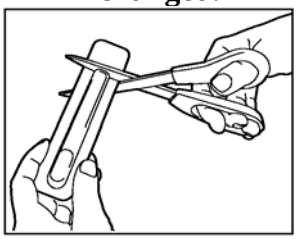
- **breast feeding.** Fentanyl passes through your breast milk and it can cause serious harm to your baby. **You should not use OTFC while breast feeding.**

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 OTFC. Sometimes, the doses of certain medicines and OTFC need to be changed if used together. **Do not take any medicine while using OTFC until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using OTFC. 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.**

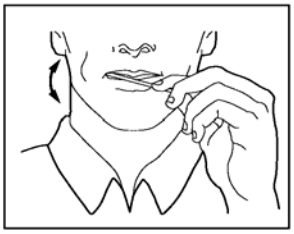
Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

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



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



- Place OTFC in your mouth between your cheeks and gums and actively suck on the medicine.
- Move OTFC around in your mouth, especially along your cheeks.
- Twirl the handle often.

  - Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
  - **Do not bite or chew OTFC. You will get less relief for your breakthrough pain.**
  - You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
  - If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth. Dispose of OTFC 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 OTFC may need to be adjusted.

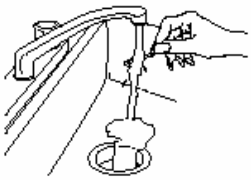
- **If you take too much OTFC or overdose, call 911 or your local emergency number for help.**

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) after use?

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC 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 OTFC 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.



5. If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the OTFC in the temporary storage bottle that you received in the OTFC Welcome Kit for safe keeping. Push the OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them.**
6. 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 OTFC units, OTFC handles, or blister packages down the toilet.

What should I avoid while taking Oral Transmucosal Fentanyl Citrate (OTFC)?

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

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

- **Do not take any medicine while using OTFC until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using OTFC. 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 Oral Transmucosal Fentanyl Citrate (OTFC)?

- **OTFC 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 OTFC?"

- **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) OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

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

- **OTFC can cause physical dependence.** Do not stop taking OTFC 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 OTFC**. 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 OTFC 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 OTFC 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 OTFC.

OTFC contains sugar. Cavities and tooth decay have occurred in patients taking OTFC**.** When taking OTFC, 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 OTFC. For a complete list, ask your doctor.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Keep OTFC 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 OTFC, get emergency help right away.**

- **OTFC is supplied in single sealed child-resistant blister packages.** Store OTFC at room temperature, 59° to 86°F (15° to 30°C) until ready to use.

- **Always keep OTFC in a secure place to protect from theft.**

How should I dispose of unopened Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

- Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed**.**

- If you are no longer using OTFC or if you have unused OTFC in your home, please follow these steps to dispose of the OTFC as soon as possible.

7. Remove all OTFC from the locked storage space.
8. Remove one OTFC unit from its blister package using scissors, and hold the OTFC by its handle over the toilet bowl.
9. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
10. Throw the handle away in a place that is out of the reach of children.
11. Repeat steps 2, 3, and 4 for each OTFC.
12. Flush the toilet twice after 5 OTFC units have been cut. Do not flush more than 5 OTFC units at a time.

- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call 1-800-896-5855.

General Information About the Safe and Effective Use of Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use OTFC only for the purpose for which it was prescribed.
Do not give OTFC to other people, even if they have the same symptoms you have.
OTFC can harm other people and even cause death.
Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your doctor. You can also ask your pharmacist or doctor for information about OTFC that is written for healthcare professionals. You can also call 1-800-896-5855.

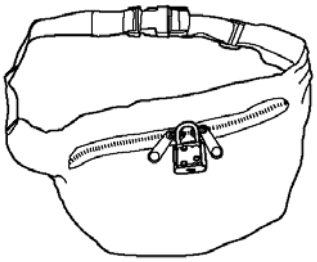
What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

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

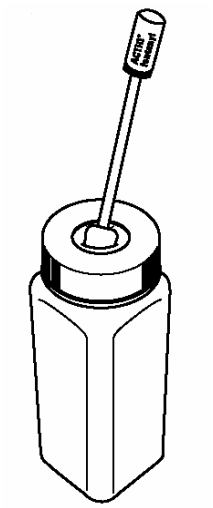
How do I use the Oral Transmucosal Fentanyl Citrate (OTFC) Welcome Kit?

- You can use the OTFC Welcome Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Welcome Kit to protect the children in your home.
- If you were not offered a Welcome Kit when you received your medicine, call 1-800-896-5855 to request one.

The OTFC Welcome Kit contains:



- A **child-resistant lock** for you to secure the storage space where you keep OTFC and any other medicines at home.
- A **portable locking pouch** for you to keep a small supply of OTFC nearby for your immediate use. The rest of your OTFC 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 OTFC unit and cannot immediately dissolve the medicine under hot tap water, immediately put the OTFC unit in the temporary storage bottle for safe keeping.
    - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.
- See “How should I dispose of unopened OTFC units when they are no longer needed?” for proper disposal of OTFC.

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

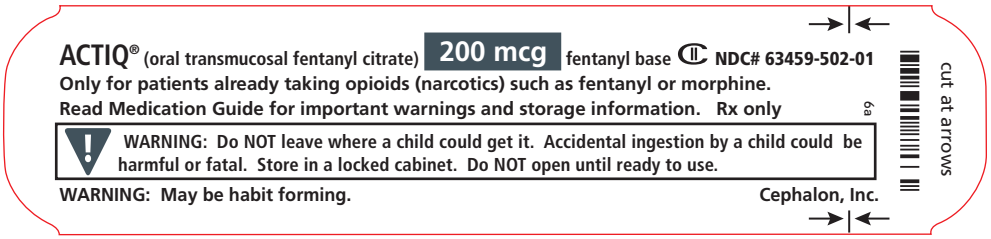
Rx Only.

Anesta Corp., Salt Lake City, UT 84116, USA

Reference Number 074000113.01
August, 2006

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

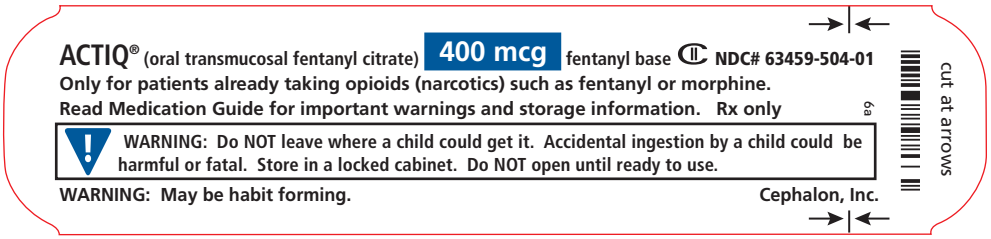
Item Number 0131 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 200 mcg Preprint Lidding
COLORS	PMS 432 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

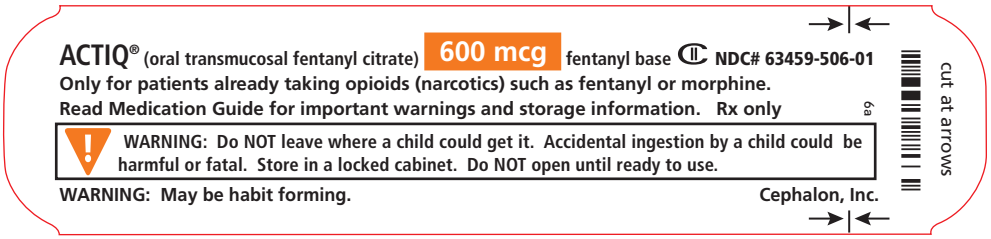
Item Number 0132 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 400 mcg Preprint Lidding
COLORS	PMS 294 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

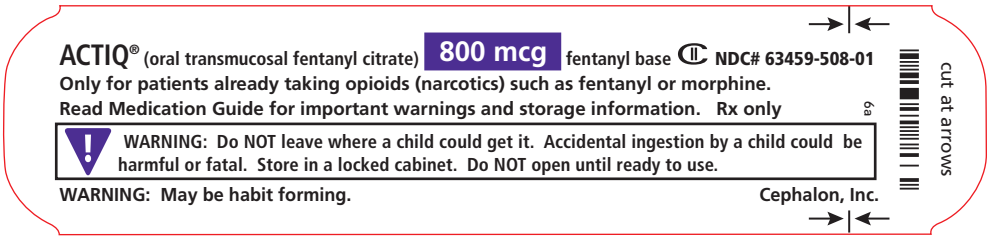
Item Number 0133 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 600 mcg Preprint Lidding
COLORS	PMS 166 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

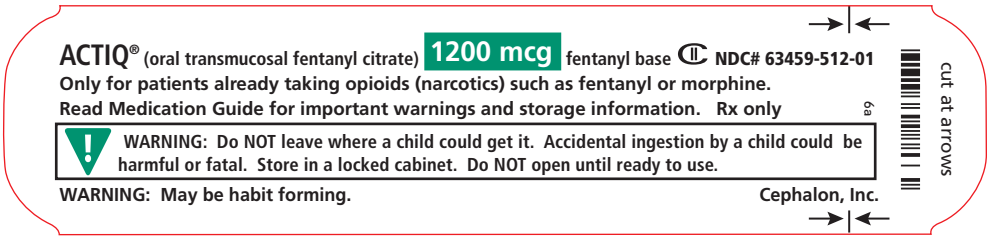
Item Number 0134 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 800 mcg Preprint Lidding
COLORS	PMS 2597 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

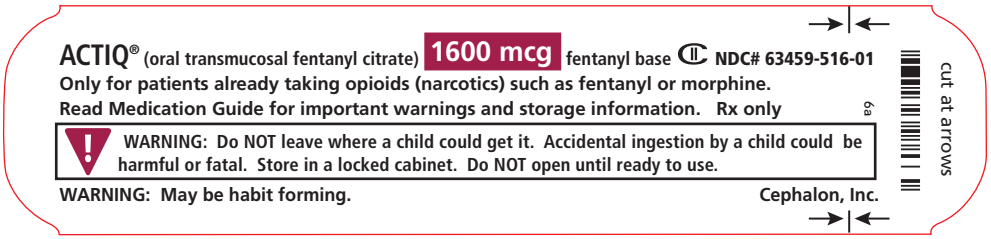
Item Number 0135 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 1200 mcg Preprint Lidding
COLORS	PMS 340 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

ACTIQ Blister Lidding

08/22/06



ARTWORK INFORMATION

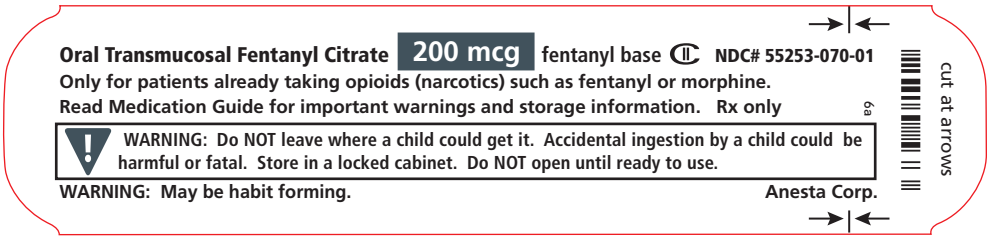
Item Number 0136 Version Number.05

SPECIFICATION

COMPONENT	ACTIQ 1200 mcg Preprint Lidding
COLORS	PMS 208 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

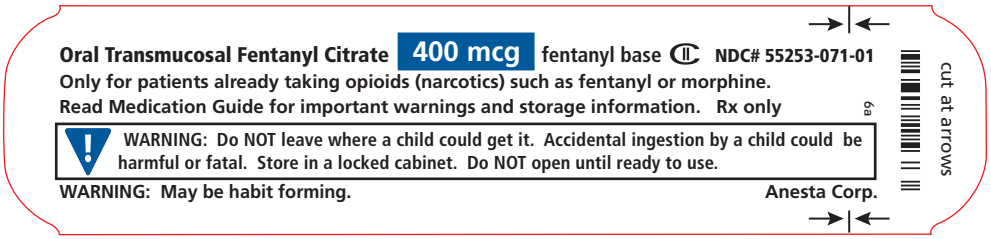
Item Number 072000014 Version Number.01

SPECIFICATION

COMPONENT	200 mcg Preprint OTFC
COLORS	PMS 432 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

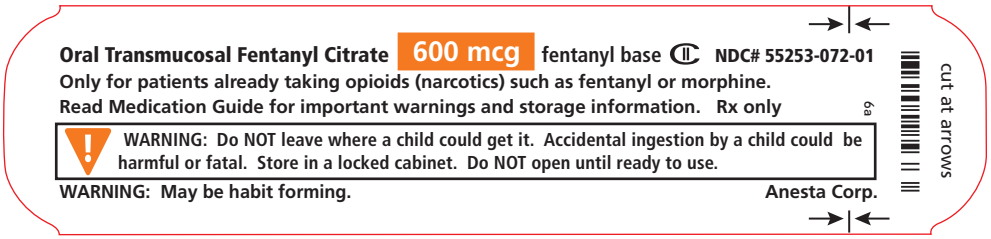
Item Number 072000015 Version Number.01

SPECIFICATION

COMPONENT	400 mcg Preprint OTFC
COLORS	PMS 294 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

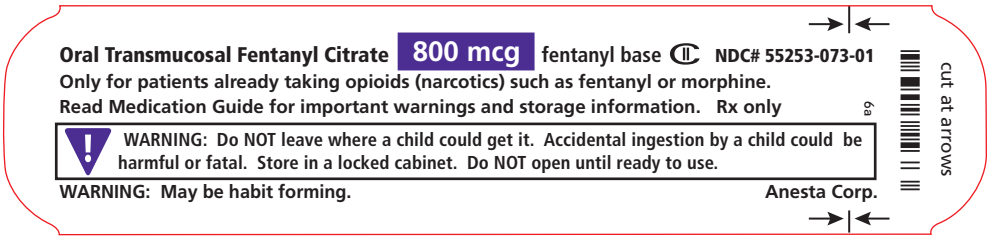
Item Number 072000016 Version Number.01

SPECIFICATION

COMPONENT	600 mcg Preprint OTFC
COLORS	PMS 166 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

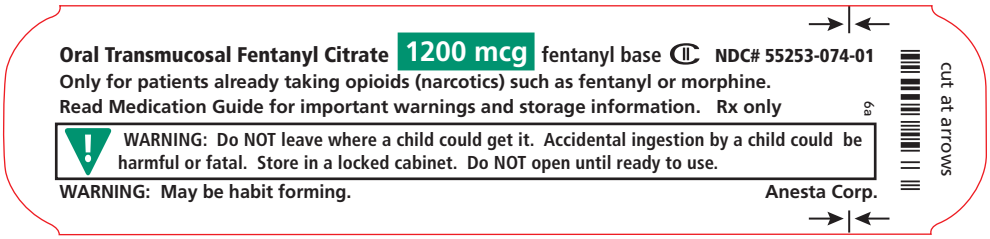
Item Number 072000017 Version Number.01

SPECIFICATION

COMPONENT	800 mcg Preprint OTFC
COLORS	PMS 2597 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

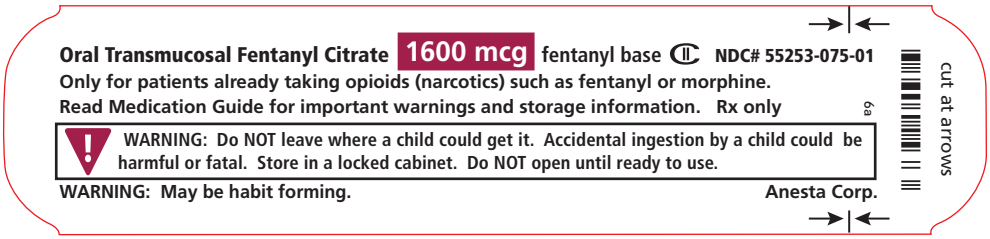
Item Number 072000018 Version Number.01

SPECIFICATION

COMPONENT	1200 mcg Preprint OTFC
COLORS	PMS 340 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

OTFC Preprint Lidding

08/22/06



ARTWORK INFORMATION

Item Number 072000019 Version Number.01

SPECIFICATION

COMPONENT	1600 mcg Preprint OTFC
COLORS	PMS 208 U - warning triangle & dosage strength rectangle Black - Text arrows & barcode
DIMENSIONS	30 mm x 130 mm

Master US Actiq Cartons version.03 08/14/06

ARTWORK INFORMATION	
Item Number 3031	Version Number .03

SPECIFICATION	
PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 200 mcg
COLORS	PMS 432 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
200 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 200 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **200 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 50230 1

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units
Cephalon
NDC 63459-502-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **200 mcg** fentanyl base

Warning: May be habit forming.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
200 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-896-5855.

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

Item # 3031.03 Printed in USA

Master US Actiq Cartons version.03 08/14/06

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
400 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 400 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **400 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 50430 5

ARTWORK INFORMATION	
Item Number 3032	Version Number .03

SPECIFICATION	
PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 400 mcg
COLORS	PMS 294 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units
Cephalon
NDC 63459-504-30
Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **400 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units
ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
400 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-896-5855.

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

Item # 3032.03 Printed in USA

Master US Actiq Cartons version.03 08/14/06

ARTWORK INFORMATION	
Item Number 3033	Version Number .03

SPECIFICATION	
PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 600 mcg
COLORS	PMS 166 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
600 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 600 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **600 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 50630 9

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units

Cephalon

NDC 63459-506-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **600 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
600 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-505-4421.

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

Item # 3033.03

Printed in USA

Master US Actiq Cartons version.03 08/14/06

ARTWORK INFORMATION	
Item Number 3034	Version Number .03

SPECIFICATION	
PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 800 mcg
COLORS	PMS 2597 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
800 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 800 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **800 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 50830 3

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units
Cephalon
NDC 63459-508-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **800 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
800 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-896-5855.

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

Item # 3034.03 Printed in USA

Master US Actiq Cartons version.03 08/14/06

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
1200 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1200 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **1200 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 51230 0

ARTWORK INFORMATION

Item Number 3035 Version Number .03

SPECIFICATION

PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 1200 mcg
COLORS	PMS 340 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units

Cephalon

NDC 63459-512-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **1200 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
1200 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-896-5855.

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

Item # 3035.03

Printed in USA

Master US Actiq Cartons version.03 08/14/06

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
1600 mcg
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1600 mcg fentanyl base, hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **1600 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed ACTIQ must be disposed of properly. Read enclosed ACTIQ Medication Guide for important warnings and directions.

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, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing ACTIQ, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the ACTIQ Medication Guide
- ☐ Discuss the ACTIQ Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

(01) 1 0363459 51630 8

ARTWORK INFORMATION

Item Number 3036 Version Number .03

SPECIFICATION

PRODUCT NAME	ACTIQ
COMPONENT	30 carton US 1600 mcg
COLORS	PMS 208 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units

Cephalon

NDC 63459-516-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to **1600 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed ACTIQ Medication Guide for important warnings and directions.

30 Units

ACTIQ®
(oral transmucosal fentanyl citrate)
equivalent to
1600 mcg
fentanyl base

To order an ACTIQ Welcome Kit, call the ACTIQ Welcome Kit Information Line: 1-800-896-5855.

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

Item # 3036.03

Printed in USA

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000165 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 200 mcg
COLORS	PMS 432 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **200 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 200 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **200 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO

(01) 1 0363459 52230 9

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units Cephalon NDC 55253-070-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **200 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **200 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000165.01 Printed in USA

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000166 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 400 mcg
COLORS	PMS 294 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **400 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 400 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **400 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO

(01) 1 0363459 52430 3

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **400 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000166.01 Printed in USA

30 Units

Cephalon

NDC 55253-071-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **400 mcg** fentanyl base

Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000167 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 600 mcg
COLORS	PMS 166 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) II

equivalent to **600 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 600 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) II

equivalent to **600 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO
(01) 1 0363459 52630 7

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units Cephalon NDC 55253-072-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate (OTFC) II

equivalent to **600 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) II

equivalent to **600 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000167.01 Printed in USA

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000168 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 800 mcg
COLORS	PMS 2597 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **800 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 800 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **800 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO
(01) 1 0363459 52830 1

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units Cephalon NDC 55253-073-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **800 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **800 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000168.01 Printed in USA

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000169 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 1200 mcg
COLORS	PMS 340 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1200 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1200 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1200 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO
(01) 1 0363459 53230 8

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

30 Units Cephalon NDC 55253-074-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1200 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1200 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000169.01 Printed in USA

Master: OTFC Cartons version.01 08/14/06

ARTWORK INFORMATION

Item Number 073000170 Version Number .01

SPECIFICATION

PRODUCT NAME	OTFC
COMPONENT	30 carton US 1600 mcg
COLORS	PMS 208 C (100%) - rectangular objects PMS 109 C (100%) - warning triangle Black - text
DIMENSIONS	Per attached 30 count die illustration

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1600 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1600 mcg fentanyl base, dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

For oral transmucosal administration. See insert for dosage and administration.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use.
(See USP Controlled Room Temperature.)

℞ only

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1600 mcg** fentanyl base

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.
Partially consumed OTFC must be disposed of properly. Read enclosed OTFC Medication Guide for important warnings and directions.

What to do if a child or an adult accidentally takes OTFC
OTFC contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed OTFC.
In these people, OTFC can cause their breathing to slow down or even stop. If you think someone has accidentally taken OTFC, follow these steps immediately:
1. Remove the OTFC unit from the person's mouth.
2. If the person is asleep, wake them up and keep them awake by calling their name and shaking their arm or shoulder.
3. **If you cannot wake them up 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.

To the Pharmacist: Before dispensing OTFC, please do the following:
- ☐ Make sure the patient is taking opioids chronically
- ☐ Counsel the patient about child safety
- ☐ Encourage the patient to read the OTFC Medication Guide
- ☐ Discuss the OTFC Welcome Kit
- ☐ Counsel the patient about disposal of partially consumed units

Place pharmacy label above

FPO
(01) 1 0363459 53630 6

30 Units

Oral Transmucosal Fentanyl Citrate (OTFC) CII

equivalent to **1600 mcg** fentanyl base

To order an OTFC Welcome Kit, call the OTFC Welcome Kit Information Line: 1-800-896-5855.

Manufactured by:
Anesta Corp.,
Salt Lake City, UT 84116

Item # 073000170.01 Printed in USA

equivalent to **1600 mcg** fentanyl base
Warning: May be habit forming.

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed OTFC Medication Guide for important warnings and directions.

30 Units Cephalon NDC 55253-075-30

Only for patients already taking opioids (narcotics) such as fentanyl or morphine.

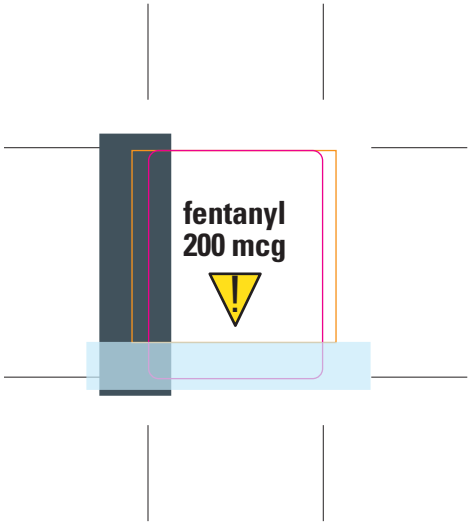
Oral Transmucosal Fentanyl Citrate (OTFC) CII

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000008.01
200 mcg
Gray = PMS 432 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

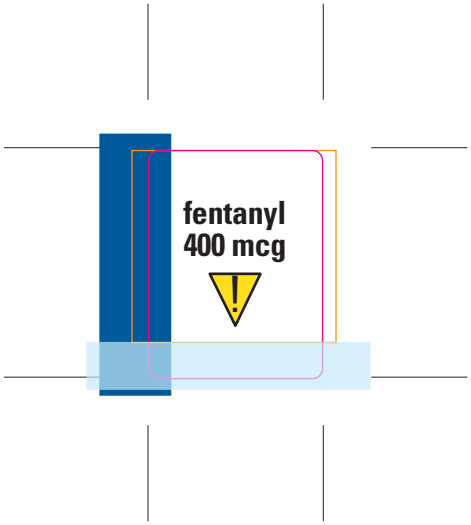
Aqueous Coat

Glue Area

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000009.01
400 mcg
Blue = PMS 294 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

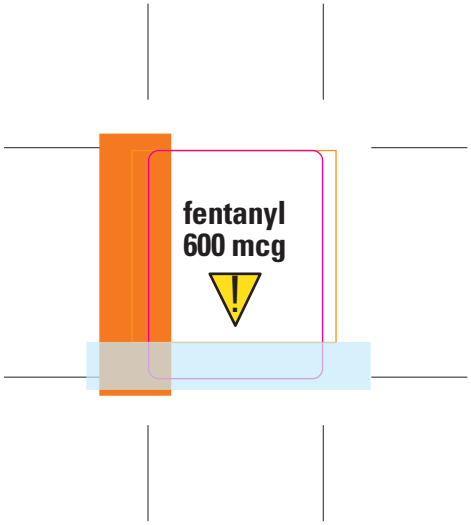
Aqueous Coat

Glue Area

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000010.01
600 mcg
Orange = PMS 166 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

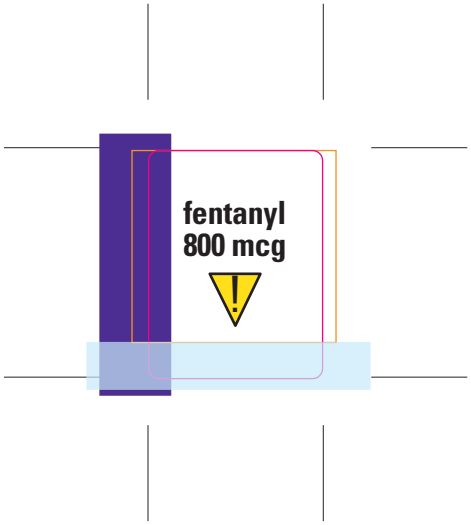
Aqueous Coat

Glue Area

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000011.01
800 mcg
Purple = PMS 2597 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

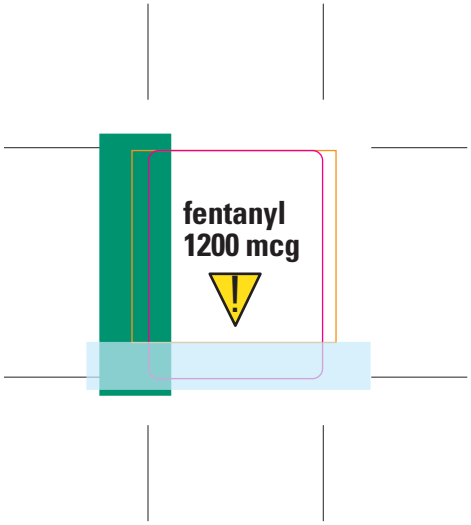
Aqueous Coat

Glue Area

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000012.01
1200 mcg
Green = PMS 340 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

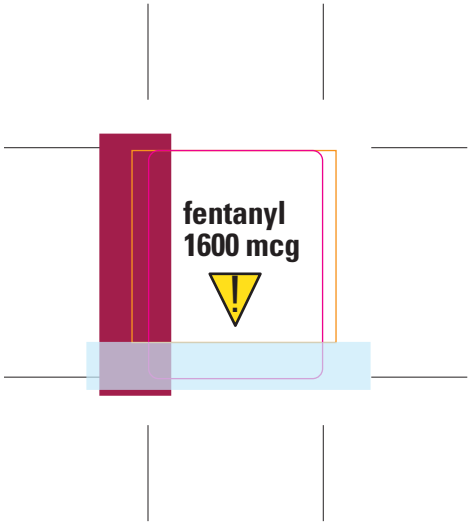
Aqueous Coat

Glue Area

Oral Transmucosal Fentanyl Citrate Handle Tag

05/11/06

Part #011000013.01
1600 mcg
Maroon = PMS 208 C
Yellow = PMS 109 C
Black text



Color Bar Width (after die cut):
3 mm - 4 mm **(not less than 3 mm, target 3 mm)**
(.12" - .16")

Die Dimensions (w x h):
22.86 mm x 30.23 mm
(.90" x 1.19")
Radius: 3.175 mm (.125")

Aqueous Coat

Glue Area