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March 7, 2005

Jialynn Wang, PharmD.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and
Communications, HFD-42
Attention: Document Control Room 17B-17
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Actiq® (oral transmucosal fentanyl citrate, OTFC®)
NDA 20-747
Promotional Material

Dear Dr. Wang

The purpose of this communication is to submit the following Actiq promotional pieces for your review:

ACTIQ Montage Booth Panels (ACT244, 245, 246, 247, 248, 249, 250, 252, 253, 256)

- Attachment 1 contains a copy of the patient booth panels (ACT244-247) followed by a copy of the associated reference;
- Attachment 2 contains a copy of the montage single booth panel (ACT248), montage horizontal booth panel (ACT253) and montage table top panel (ACT252) followed by a copy of the associated reference;
- Attachment 3 contains a copy of the montage journal ad booth panel (ACT256) followed by a copy of the associated references;
- Attachment 4 contains a copy of the "Actiq at Work" booth panel and table top panel (ACT250) followed by a copy of the associated reference;
- Attachment 5 contains a copy of the mountain graph booth panel (ACT249) followed by a copy of the associated reference.

These panels were developed based on a previously approved promotional pieces; ACTIQ Patient Profiles (MACMIS #12674), Montage Journal Ad, and ACTIQ Detail Aid (MACMIS #12800). Your approval of these materials can be found on

letters dated November 24, 2004 and September 29, 2004 which are provided in Attachment 6.

ACTIQ Montage Core Sales Aid (ACT254)

- Attachment 7 contains a color copy of this piece along with copies of references for this piece.

This sales aid is a combination of the previously approved Montage Journal Ad and Actiq Sales with virtually no changes. Your approval letter for these pieces (MACMIS No. 12800) is dated November 24, 2004 and is provided in Attachment 6.

ACTIQ Product Return Sheet (ACT243)

- The Product Return Sheet (Attachment 8) will be available in a tear pad format. Each pad will contain 25 sheets with the package insert as the last 4 sheets of the tear pad. The pads will be printed in black and white and individually packaged with a sticker label that states "Please see accompanying full prescribing information, including Boxed Warning."

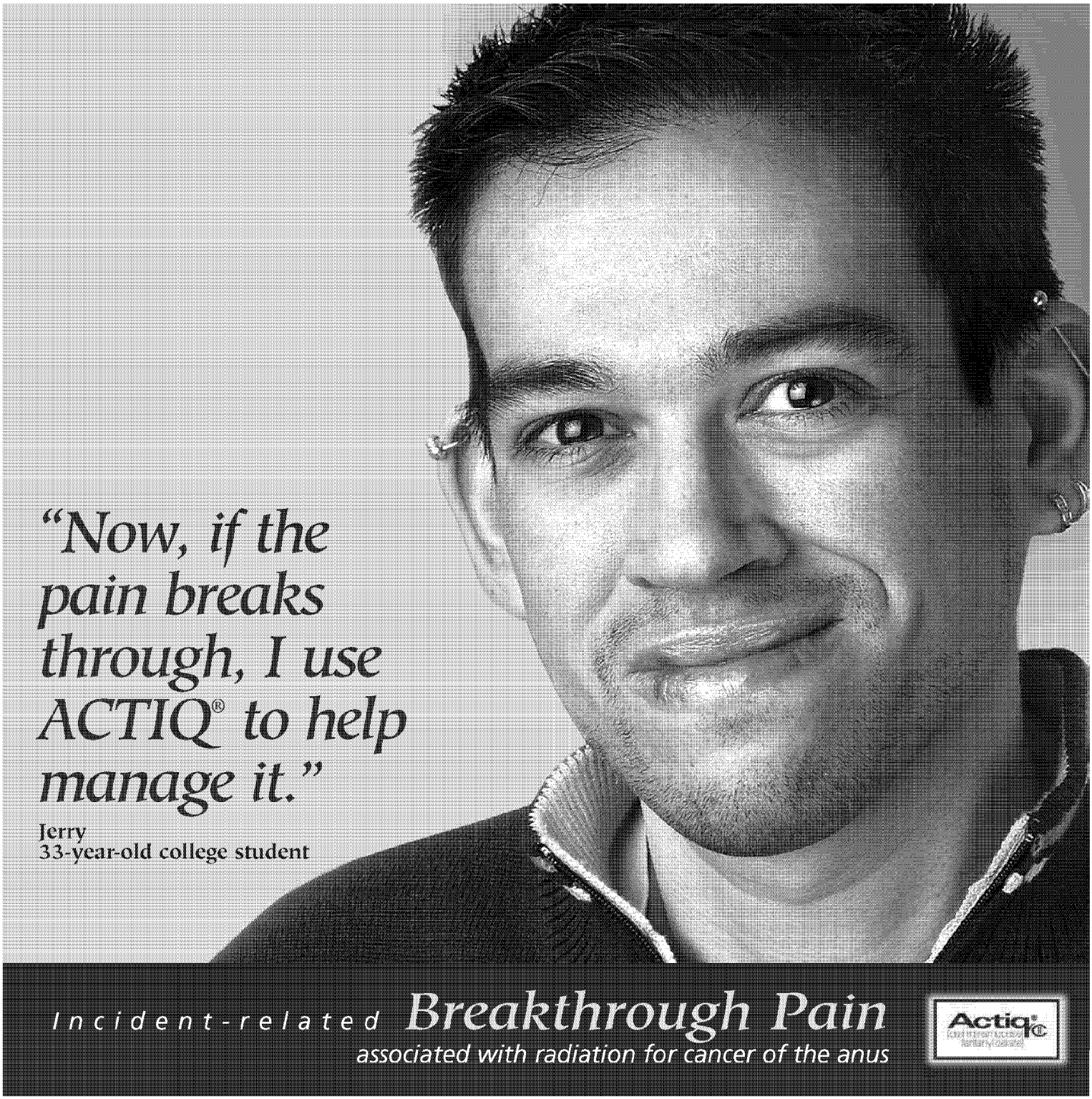
Pursuant to 21 CFR 314.550, we are submitting this material 35 days prior to the intended time of initial dissemination in order to accommodate for the receipt time by the Agency and the 30-day review time. It is our intent to disseminate this piece on or after **April 11, 2005**.

If you have any questions regarding this submission, please contact me by telephone at (610) 738-6237. Alternatively, our facsimile number is (610) 738-6642 and my e-mail is cmarchio@cephalon.com.

Sincerely,

Carol S. Marchione

Carol S. Marchione
Senior Director
Regulatory Affairs



Incident-related **Breakthrough Pain**
associated with radiation for cancer of the anus

Actiq®

- The ACTIQ unit should not be chewed or swallowed as that might result in lower peak concentrations and bioavailability than when consumed as directed[1]
- Both the blood fentanyl profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed[1]

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Individual results may vary. Once a successful dose has been found, patients should limit their consumption to 4 or fewer units per day.

Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT244

Neuropathic Breakthrough Pain

associated with lung cancer

Actiq®

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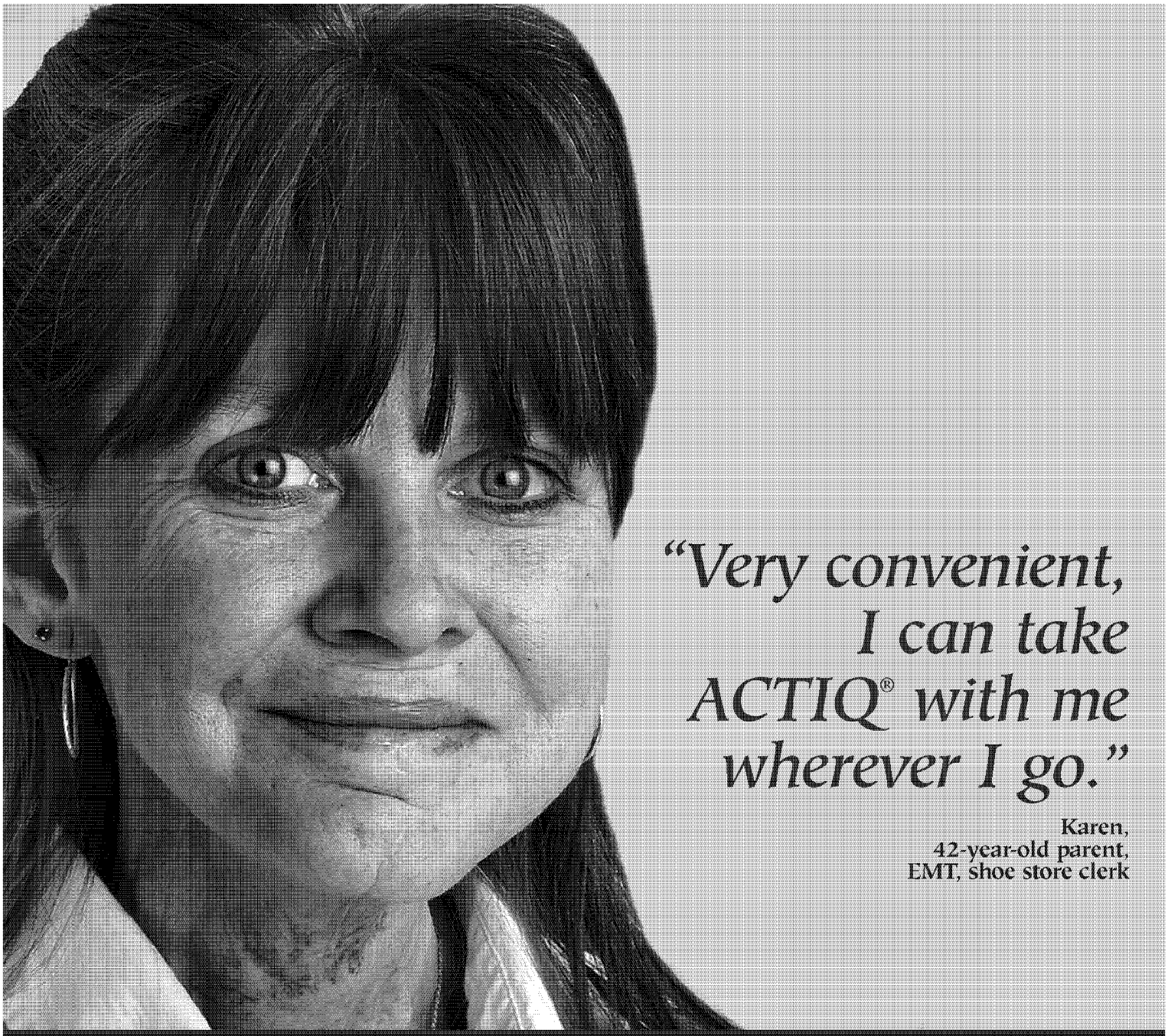
Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT245



Activity-related **Breakthrough Pain**
in a cancer patient with mucositis

Actiq®

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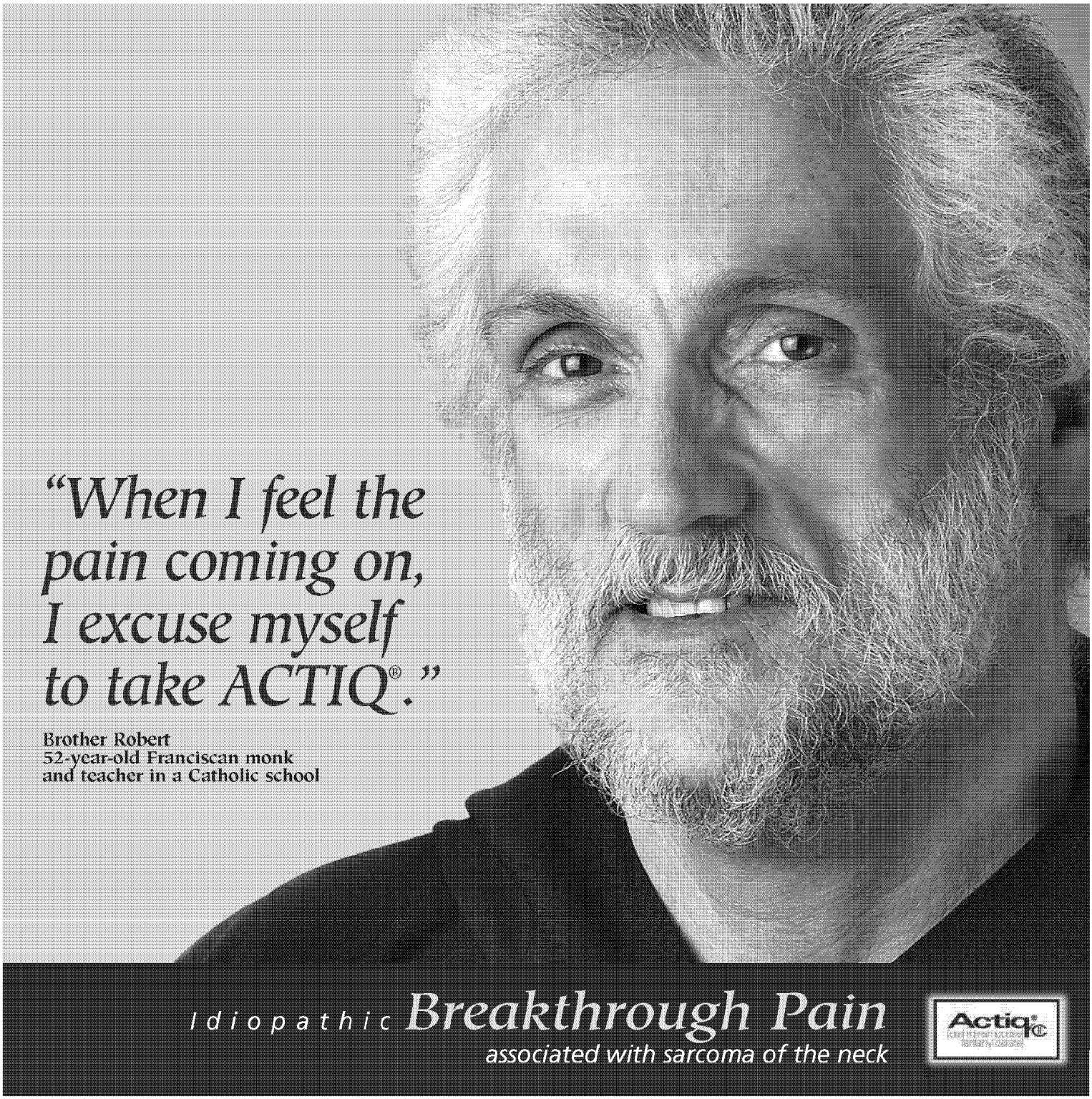
Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT246



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Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT247

ACTIQ®

(oral transmucosal fentanyl citrate)

CII

1598.02

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

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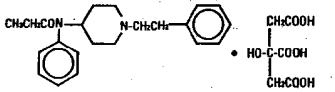
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

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

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

Clinical Pharmacology

Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

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

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

Respiratory System:

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

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

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

Pharmacokinetics

Absorption:

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

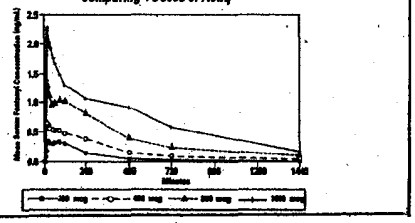
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

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

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ 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	800 mcg	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 (28)	0.76 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (% CV)	102 (66)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (% CV)	193 (48)	386 (115)	361 (55)	358 (45)

Distribution:

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism:

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

Elimination:

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

Special Populations:

Elderly Patients:

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

Patients with Renal or Hepatic Impairment:

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

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

Gender

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

CLINICAL TRIALS

Breakthrough Cancer Pain:

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered

(200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

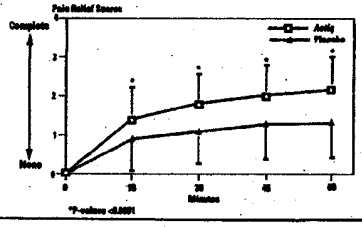
Table 2
Successful Dose of Actiq Following Initial Titration

Actiq Dose	Total No (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean ±SD	789±468 mcg

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

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

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



*P-values <0.0001

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

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see **DOSAGE AND ADMINISTRATION**).

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

CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

WARNINGS

See BOX WARNING

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

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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

PRECAUTIONS

General

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

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

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

Hypoventilation (Respiratory Depression)

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS,** and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking *Actiq* (see **ADVERSE REACTIONS** - Post-Marketing Experience). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

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

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

Disposal of Used *Actiq* Units

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

1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened *Actiq* Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

1) Remove the *Actiq* unit from its blister package using scissors, and hold the *Actiq* by its handle over the toilet bowl.
2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3) Dispose of the handle in a place that is out of the reach of children.
4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, blister packages, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

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

Laboratory Tests

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

Drug Interactions

See **WARNINGS**.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy - Category C

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Actiq is not indicated for use in labor and delivery.

Nursing Mothers

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

Pediatric Use

See WARNINGS.

Geriatric Use

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

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

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

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

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

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

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

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

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of *Actiq* that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.

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

Dose Group	200-800 mcg	801-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	230	138	84	41	254
Body As A Whole					
Asthenia	6	4	6	7	9
Headache	5	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	19	11	32	20
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	1
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

The following adverse events not reflected in Table 3 occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 4 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse events are listed in descending order of frequency within each body system.

Table 4.

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

Dose Group	200-800 mcg	801-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	88	53	83	27	152
Body As A Whole					
Asthenia	25	30	17	15	28
Headache	12	17	13	4	18
Accidental Injury	4	8	4	7	8
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	38	25	26	46
Vomiting	24	26	19	7	32
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	19	6	0	16
Anxiety	9	6	6	7	15
Somnolence	8	13	5	7	15
Confusion	3	8	13	7	10
Depression	9	6	2	7	9
Insomnia	8	4	6	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	11	16	8	7	22
Skin					
Rash	3	6	0	4	6
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

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

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to *Actiq*.

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

OVERDOSAGE

Clinical Presentation

The manifestations of *Actiq* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

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

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

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

Treatment of Overdose in Opioid-Tolerant Patients

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

General Considerations for Overdose

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

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

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

DOSAGE AND ADMINISTRATION

***Actiq* is contraindicated in non-opioid tolerant individuals.**

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

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

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

Administration of *Actiq*

The blister package should be opened with scissors immediately prior to product use. The patient should place the *Actiq* unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The *Actiq* unit should be sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The *Actiq* unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in *Actiq* clinical trials. If signs of excessive opioid effects appear before the unit is consumed, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

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

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

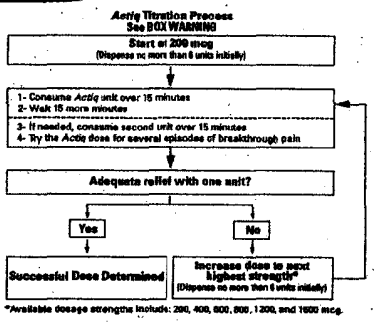
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



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

Dosage Adjustment

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

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

Discontinuation of *Actiq*

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

SAFETY AND HANDLING

Actiq is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see **BOX WARNING, WARNINGS, PRECAUTIONS** and **PATIENT LEAFLET**).

Store at 20-25°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.)

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

DISPOSAL OF ACTIQ

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

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

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

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

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

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

℞ only.

DEA order form required. A Schedule CII narcotic.

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

U.S. Patent Nos. 4,671,953; 4,863,737; and 5,785,989
Printed in USA

#1598.02

When onset matters... ACTIQ® responds.

A significant benefit of ACTIQ is its time to onset of analgesia

With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit.[1]

Actiq®

- The ACTIQ unit should not be chewed or swallowed as that might result in lower peak concentrations and bioavailability than when consumed as directed[1]
- Both the blood fentanyl profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed[1]

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT248

When onset matters... ACTIQ® responds.

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With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit.[1]

Actiq® (oral transmucosal fentanyl citrate) C-II

Relief at hand

- The most serious adverse events associated with opioids are respiratory depression, circulatory depression, hypotension, and shock
- The adverse events seen with ACTIQ are typical opioid side effects, and include somnolence, nausea, vomiting, and dizziness

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT253

When onset matters... ACTIQ® responds.

A significant benefit of ACTIQ is its time to onset of analgesia

With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit.[1]

Actiq®

- The ACTIQ unit should not be chewed or swallowed as that might result in lower peak concentrations and bioavailability than when consumed as directed[1]
- Both the blood fentanyl profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed[1]

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Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT252

ACTIQ®

(oral transmucosal fentanyl citrate)

CII

1598.02

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

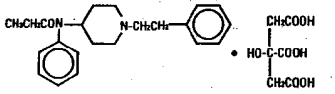
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

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

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

Clinical Pharmacology

Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

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

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

Respiratory System:

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

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

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

Pharmacokinetics

Absorption:

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

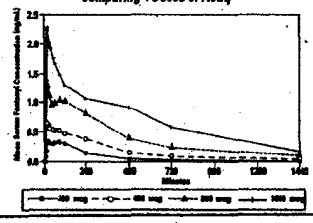
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

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

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ 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	800 mcg	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 (28)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (% CV)	102 (66)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (% CV)	193 (48)	386 (115)	361 (55)	358 (45)

Distribution:

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism:

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

Elimination:

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

Special Populations:

Elderly Patients:

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

Patients with Renal or Hepatic Impairment:

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

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

Gender

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

CLINICAL TRIALS

Breakthrough Cancer Pain:

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered

(200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

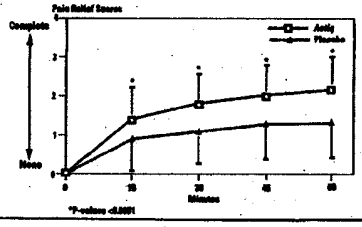
Table 2
Successful Dose of Actiq Following Initial Titration

Actiq Dose	Total No (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean ±SD	789±468 mcg

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

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

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



*P-values <0.0001

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

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see **DOSAGE AND ADMINISTRATION**).

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

CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

WARNINGS

See BOX WARNING

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

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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

PRECAUTIONS

General

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

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

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

Hypoventilation (Respiratory Depression)

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS,** and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking *Actiq* (see **ADVERSE REACTIONS** - Post-Marketing Experience). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

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

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

Disposal of Used *Actiq* Units

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

1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened *Actiq* Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

1) Remove the *Actiq* unit from its blister package using scissors, and hold the *Actiq* by its handle over the toilet bowl.
2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3) Dispose of the handle in a place that is out of the reach of children.
4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, blister packages, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

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

Laboratory Tests

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

Drug Interactions

See **WARNINGS**.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy - Category C

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Actiq is not indicated for use in labor and delivery.

Nursing Mothers

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

Pediatric Use

See WARNINGS.

Geriatric Use

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

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

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

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

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

The adverse events seen with *Actiq* are typical opioid side effects. ~~Frequently, these adverse events will cease or decrease in intensity with continued use of *Actiq*, as the patient~~ is titrated to the proper dose. Opioid side effects should be expected and managed accordingly. ~~The most serious adverse effects associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.~~ All patients should be followed for symptoms of respiratory depression.

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

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of *Actiq* that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.

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

Dose Group	200-600 mcg	800-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	230	138	64	41	254
Body As A Whole					
Asthenia	6	4	0	7	5
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	25	11	22	23
Vomiting	7	8	0	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	6	5	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

The following adverse events not reflected in Table 3 occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 4 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse events are listed in descending order of frequency within each body system.

Table 4.

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

Dose Group	200-600 mcg	800-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	[illegible]	83	83	27	152
Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	0	4	7	9
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	30	25	25	46
Vomiting	21	20	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	0	0	16
Anxiety	9	6	8	7	16
Somnolence	8	13	5	7	15
Confusion	2	6	13	7	10
Depression	9	4	2	7	9
Insomnia	9	1	6	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	0	4	3
Sweating	3	2	2	4	0
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

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

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to *Actiq*.

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

OVERDOSAGE

Clinical Presentation

The manifestations of *Actiq* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

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

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

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

Treatment of Overdose in Opioid-Tolerant Patients

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

General Considerations for Overdose

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

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

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

DOSAGE AND ADMINISTRATION

***Actiq* is contraindicated in non-opioid tolerant individuals.**

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

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

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

Administration of *Actiq*

The blister package should be opened with scissors immediately prior to product use. The patient should place the *Actiq* unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The *Actiq* unit should be sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The *Actiq* unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in *Actiq* clinical trials. If signs of excessive opioid effects appear before the unit is consumed, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

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

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

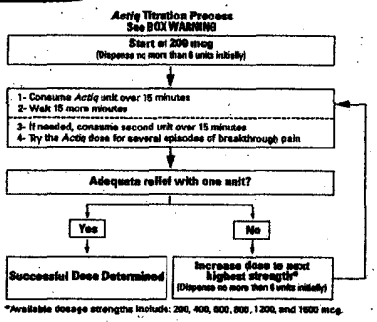
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



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

Dosage Adjustment

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

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

Discontinuation of *Actiq*

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

SAFETY AND HANDLING

Actiq is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see **BOX WARNING, WARNINGS, PRECAUTIONS** and **PATIENT LEAFLET**).

Store at 20-25°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.)

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

DISPOSAL OF ACTIQ

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

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

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

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

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

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

℞ only.

DEA order form required. A Schedule CII narcotic.

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

U.S. Patent Nos. 4,671,953; 4,863,737; and 5,785,989
Printed in USA

#1598.02

When onset matters... ACTIQ® responds.

A significant benefit of ACTIQ is its time to onset of analgesia

With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit.[1]

- The unique oral transmucosal delivery system (OTS™) allows fentanyl to rapidly dissolve into the highly permeable and well-vascularized oral mucosa
- High lipophilicity of oral transmucosal fentanyl allows for rapid absorption across the oral mucosa into the blood and distribution into the CNS—a process with a 3- to 5-minute half-life[1]
- A portion of the fentanyl is swallowed and slowly absorbed through the GI tract[1]

Longer or shorter consumption times than the recommended 15 minutes may produce less efficacy than reported in clinical trials.

Side effect profile

- The most serious adverse events associated with opioids are respiratory depression, circulatory depression, hypotension, and shock[1]
- The adverse events seen with ACTIQ are typical opioid side effects, and include somnolence, nausea, vomiting, and dizziness
- Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose[1]

Portability, convenience, and experience

- Patients can use ACTIQ anywhere as soon as they begin to feel breakthrough cancer pain. Patients should not eat or drink anything while taking ACTIQ
- Over 48 million units have been prescribed[2]

Actiq® (oral transmucosal fentanyl citrate) CII

Relief at hand

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Please see boxed warning and brief summary of prescribing information on adjacent pages.
For more information, please call Cephalon Professional Services at 1-800-896-5855.

References: 1. ACTIQ Package Insert. Rev. August 2004. 2. IMS HEALTH® National Prescription Audit Plus™ (April 1999-June 2004).

ACT256

ACTIQ®

(oral transmucosal fentanyl citrate)

CII

1598.02

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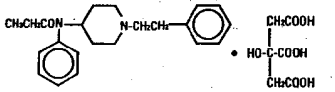
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

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

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

Clinical Pharmacology

Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

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

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

Respiratory System:

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

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

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

Pharmacokinetics

Absorption:

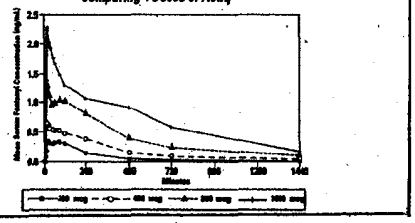
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary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

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

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

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ 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	800 mcg	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 (28)	0.76 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (% CV)	102 (66)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (% CV)	193 (48)	386 (115)	361 (55)	358 (45)

Distribution:

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism:

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

Elimination:

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

Special Populations:

Elderly Patients:

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

Patients with Renal or Hepatic Impairment:

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

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

Gender

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

CLINICAL TRIALS

Breakthrough Cancer Pain:

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered

(200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

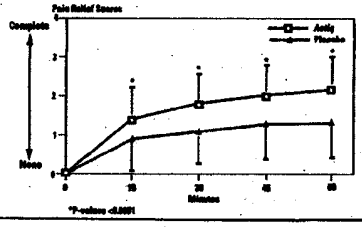
Table 2
Successful Dose of Actiq Following Initial Titration

Actiq Dose	Total No (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean ±SD	789±468 mcg

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

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

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



*P-values <.0001

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

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see **DOSAGE AND ADMINISTRATION**).

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

CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

WARNINGS

See BOX WARNING

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

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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

PRECAUTIONS

General

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

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

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

Hypoventilation (Respiratory Depression)

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS,** and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking *Actiq* (see **ADVERSE REACTIONS** - Post-Marketing Experience). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

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

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

Disposal of Used *Actiq* Units

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

1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened *Actiq* Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

1) Remove the *Actiq* unit from its blister package using scissors, and hold the *Actiq* by its handle over the toilet bowl.
2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3) Dispose of the handle in a place that is out of the reach of children.
4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, blister packages, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

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

Laboratory Tests

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

Drug Interactions

See **WARNINGS**.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy - Category C

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Actiq is not indicated for use in labor and delivery.

Nursing Mothers

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

Pediatric Use

See WARNINGS.

Geriatric Use

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

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

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

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

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

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

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

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

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of *Actiq* that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.

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

Dose Group	200-800 mcg	801-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	230	138	94	41	254
Body As A Whole					
Asthenia	6	4	6	7	9
Headache	5	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	19	11	32	20
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	5	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

The following adverse events not reflected in Table 3 occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 4 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse events are listed in descending order of frequency within each body system.

Table 4.

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

Dose Group	200-800 mcg	801-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	86	53	53	27	152
Body As A Whole					
Asthenia	25	30	17	15	28
Headache	12	17	13	4	18
Accidental Injury	4	6	4	7	8
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	38	25	26	46
Vomiting	21	26	15	7	32
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	19	6	0	16
Anxiety	9	6	6	7	15
Somnolence	6	13	6	7	15
Confusion	3	6	13	7	10
Depression	9	6	2	7	9
Insomnia	9	4	6	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	15	8	7	22
Skin					
Rash	3	6	0	4	6
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

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

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to *Actiq*.

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

OVERDOSAGE

Clinical Presentation

The manifestations of *Actiq* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

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

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

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

Treatment of Overdose in Opioid-Tolerant Patients

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

General Considerations for Overdose

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

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

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

DOSAGE AND ADMINISTRATION

***Actiq* is contraindicated in non-opioid tolerant individuals.**

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

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

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

Administration of *Actiq*

The blister package should be opened with scissors immediately prior to product use. The patient should place the *Actiq* unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The *Actiq* unit should be sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The *Actiq* unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in *Actiq* clinical trials. If signs of excessive opioid effects appear before the unit is consumed, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

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

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

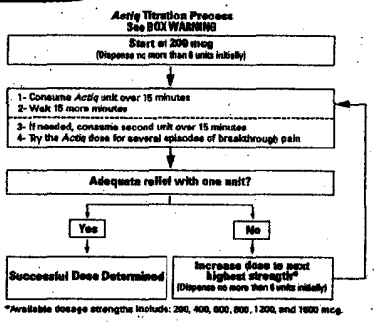
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



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

Dosage Adjustment

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

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

Discontinuation of *Actiq*

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

SAFETY AND HANDLING

Actiq is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see **BOX WARNING, WARNINGS, PRECAUTIONS** and **PATIENT LEAFLET**).

Store at 20-25°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.)

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

DISPOSAL OF ACTIQ

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

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

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

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

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

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

℞ only.

DEA order form required. A Schedule CII narcotic.

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

U.S. Patent Nos. 4,671,953; 4,863,737; and 5,785,989
Printed in USA

#1598.02

Printed in USA

#8

MTH/MAR/ 04 Ex Units TRX	Ex Units TRX Month/5/20 04	Ex Units TRX Month/6/20 04	Total Units since launch
2,297,598	2,162,718	2,280,708	48,731,712
154,395	142,030	163,789	4,468,811
481,278	477,925	500,854	11,288,359
361,034	329,411	316,425	7,462,570
600,105	552,028	586,245	12,036,539
390,216	365,583	378,069	7,605,791
310,570	295,741	335,326	5,869,642

ACTIQ	48,731,712
200MCG	4,468,811
400MCG	11,288,359
1600MC	7,462,570
800MCG	12,036,539
600MCG	7,605,791
1200MC	5,869,642

Variable : Ex Units TRX (Absolute)

		Ex Units TRX MTH/APR/99	Ex Units TRX MTH/MAY/99	Ex Units TRX MTH/JUN/99	Ex Units TRX MTH/JUL/99	Ex Units TRX MTH/AUG/99	Ex Units TRX MTH/SEP/99
ACTIQ	CEH 99/04	2,765	4,668	11,959	12,470	15,368	22,141
200MCG		2,004	2,410	5,398	4,551	4,041	7,034
400MCG		472	1,093	2,522	2,778	5,032	6,917
1600MC		0	804	1,542	2,168	1,159	1,770
800MCG		0	0	1,547	1,874	2,540	4,415
600MCG		289	260	788	564	2,195	1,414
1200MC		0	101	162	535	401	591

Ex Units TRX MTH/OCT/99	Ex Units TRX MTH/NOV/99	Ex Units TRX MTH/DEC/99	Ex Units TRX MTH/JAN/00	Ex Units TRX MTH/FEB/00	Ex Units TRX MTH/MAR/00	Ex Units TRX MTH/APR/00	Ex Units TRX MTH/MAY/00	Ex Units TRX MTH/JUN/00
25,670	35,162	41,219	41,290	48,005	79,274	71,306	88,786	104,363
7,024	8,432	10,964	10,546	10,070	16,756	13,967	14,326	16,427
10,380	9,940	11,012	10,268	14,704	17,070	15,851	17,627	21,697
901	1,766	3,665	5,187	5,211	11,038	7,848	12,142	15,599
3,126	7,649	6,407	6,913	7,532	13,048	13,377	20,305	23,599
3,779	5,493	7,927	5,400	7,944	12,641	11,270	15,225	11,734
460	1,882	1,244	2,976	2,544	8,721	8,993	9,161	15,307

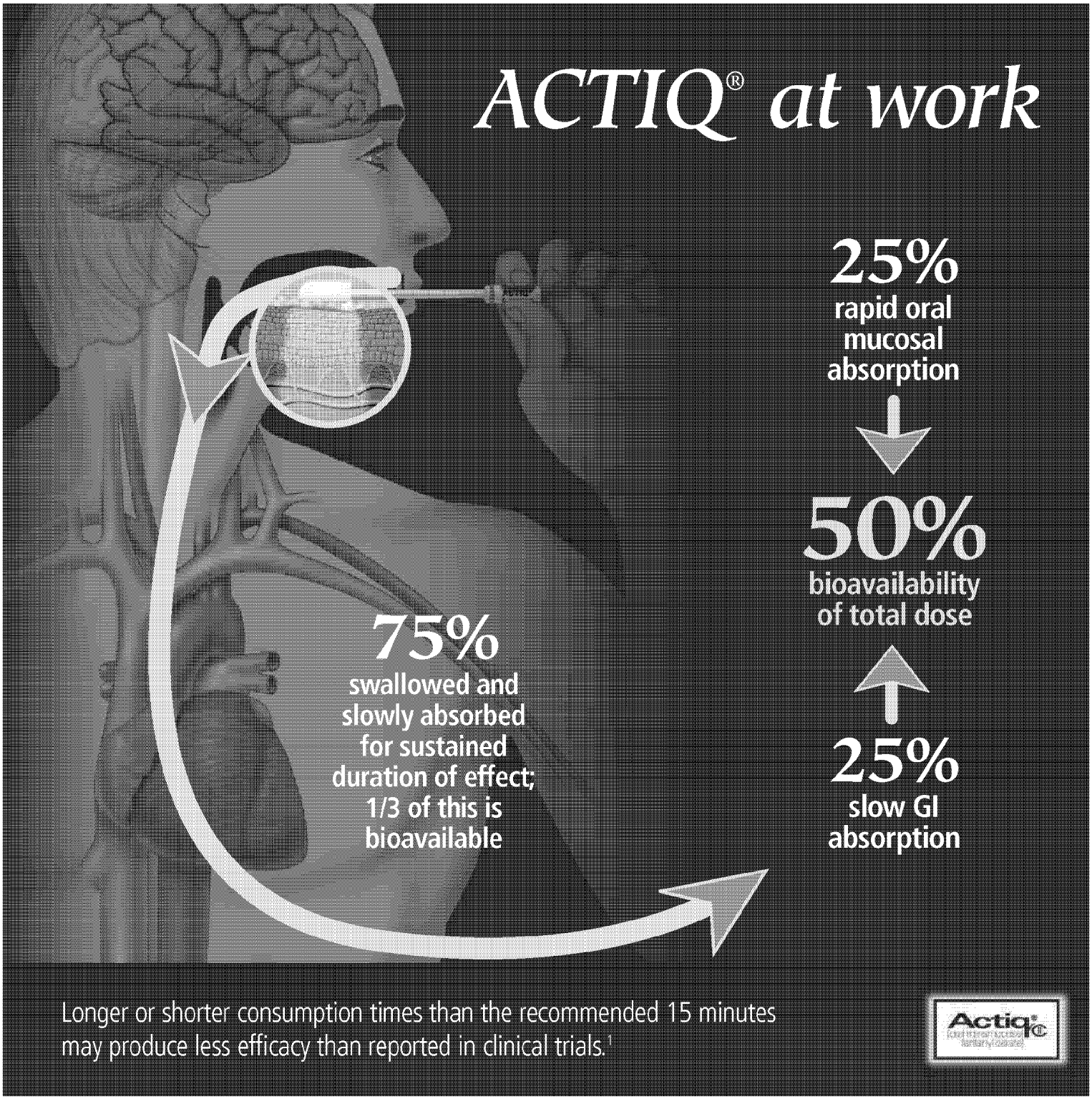
Ex Units TRX MTH/JUL/00	Ex Units TRX MTH/AUG/00	Ex Units TRX MTH/SEP/00	Ex Units TRX MTH/OCT/00	Ex Units TRX MTH/NOV/00	Ex Units TRX MTH/DEC/00	Tot Ex Units MTH/JAN/01	Tot Ex Units MTH/FEB/01	Tot Ex Units MTH/MAR/01
102,639	120,297	123,926	145,597	146,191	164,670	183,024	186,240	286,128
17,159	22,000	26,942	22,111	24,970	23,961	32,472	30,096	46,032
22,564	26,436	21,125	25,756	29,322	28,944	39,720	39,936	62,568
17,961	20,170	21,589	39,031	35,961	51,907	31,944	34,368	60,984
18,882	22,887	22,488	24,599	28,791	27,608	38,328	38,232	49,968
11,945	12,690	17,999	17,292	14,704	18,852	20,712	19,224	31,536
14,128	16,114	13,783	16,808	12,443	13,398	19,848	24,384	35,040

Tot Ex Units MTH/APR/01	Tot Ex Units MTH/MAY/01	Tot Ex Units MTH/JUN/01	Tot Ex Units MTH/JUL/01	Tot Ex Units MTH/AUG/01	Tot Ex Units MTH/SEP/01	Tot Ex Units MTH/OCT/01	Tot Ex Units MTH/NOV/01	Tot Ex Units MTH/DEC/01
248,664	275,832	383,880	380,712	394,968	534,840	478,152	539,544	706,536
44,856	46,248	62,040	59,616	61,536	74,904	65,568	67,992	87,096
54,672	62,496	95,616	98,928	104,208	140,928	135,144	143,640	198,576
46,032	53,472	72,072	63,720	68,880	91,848	81,840	90,456	112,440
45,552	53,424	71,208	71,928	78,048	108,312	99,912	120,672	155,736
29,544	32,160	41,376	46,656	46,416	64,056	56,832	73,296	97,200
28,008	28,032	41,568	39,864	35,880	54,792	38,856	43,488	55,488

Tot Ex Units MTH/JAN/02	Tot Ex Units MTH/FEB/02	Tot Ex Units MTH/MAR/02	Tot Ex Units MTH/APR/02	Tot Ex Units MTH/MAY/02	Tot Ex Units MTH/JUN/02	Tot Ex Units MTH/JUL/02	Tot Ex Units MTH/AUG/02	Tot Ex Units MTH/SEP/02
626,520	631,632	850,632	733,056	794,640	1,095,168	965,952	973,968	1,315,608
81,144	77,784	94,248	79,560	86,184	115,080	91,032	93,480	117,840
167,472	162,984	217,008	192,600	205,416	280,896	248,616	233,904	319,848
104,832	91,200	132,720	111,720	119,256	151,464	138,648	143,472	198,480
134,808	147,144	197,808	166,536	188,112	262,056	243,816	240,888	330,888
78,840	91,320	122,208	110,400	117,744	171,864	145,008	151,656	206,064
59,424	61,200	86,640	72,240	77,928	113,808	98,832	110,568	142,488

Tot Ex Units MTH/OCT/ 02	Tot Ex Units MTH/NOV/ 02	Tot Ex Units MTH/DEC/ 02	Tot Ex Units MTH/JAN/0 3	Tot Ex Units MTH/FEB/0 3	Tot Ex Units MTH/MAR/0 3	Tot Ex Units MTH/APR/ 03	MTH/MAY/ 03 Ex Units TRX
1,079,592	1,163,040	1,526,904	1,303,536	1,307,952	1,720,968	1,391,280	1,504,967
97,920	111,360	131,688	114,216	109,320	143,664	118,320	131,877
259,560	275,064	342,480	303,504	289,200	391,944	318,408	343,997
162,408	170,352	240,504	201,168	213,168	268,152	209,376	215,734
270,552	291,384	398,520	326,280	338,160	445,920	368,232	397,422
169,464	183,384	229,824	198,792	193,680	260,376	209,664	238,865
119,688	131,496	183,888	159,576	164,424	210,912	167,280	177,072

MTH/JUN/03 Ex Units TRX	MTH/JUL/03 Ex Units TRX	MTH/AUG/03 Ex Units TRX	MTH/SEP/03 Ex Units TRX	MTH/OCT/03 Ex Units TRX	MTH/NOV/03 Ex Units TRX	MTH/DEC/03 Ex Units TRX	MTH/JAN/04 Ex Units TRX	MTH/FEB/04 Ex Units TRX
1,560,651	1,725,137	1,789,134	1,825,270	1975746	1792203	2211574	2108175	2011097
127,006	141,593	142,358	143,699	147446	129627	145604	151313	135685
352,705	397,386	413,879	415,404	461329	413902	458859	455650	428345
228,260	241,124	252,686	256,963	279869	268580	357295	314871	317923
415,244	471,526	471,228	451,800	488523	436769	569028	531672	524938
247,006	276,095	296,323	312,598	348720	302967	372939	363754	332955
190,430	197,413	212,660	244,806	249859	240358	307849	290915	271251



- The ACTIQ unit should not be chewed or swallowed as that might result in lower peak concentrations and bioavailability than when consumed as directed[1]
- Both the blood fentanyl profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed[1]

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. ACTIQ Package Insert. Rev. August 2004.

ACT250

ACTIQ®

(oral transmucosal fentanyl citrate)

CII

1598.02

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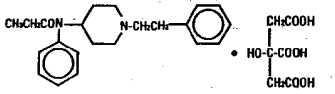
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

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

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

Clinical Pharmacology

Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

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

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

Respiratory System:

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

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

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

Pharmacokinetics

Absorption:

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

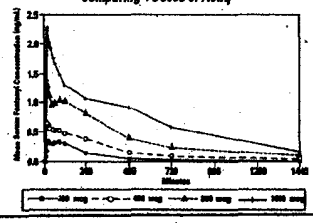
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

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

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ 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	800 mcg	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 (28)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (% CV)	102 (66)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (% CV)	193 (48)	386 (115)	361 (55)	358 (45)

Distribution:

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism:

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

Elimination:

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

Special Populations:

Elderly Patients:

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

Patients with Renal or Hepatic Impairment:

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

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

Gender

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

CLINICAL TRIALS

Breakthrough Cancer Pain:

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered

(200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

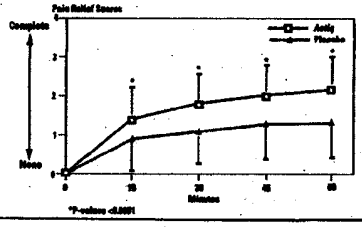
Table 2
Successful Dose of Actiq Following Initial Titration

Actiq Dose	Total No (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean ±SD	789±468 mcg

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

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

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



*P-values <.0001

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

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see **DOSAGE AND ADMINISTRATION**).

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

CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

WARNINGS

See BOX WARNING

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

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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

PRECAUTIONS

General

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

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

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

Hypoventilation (Respiratory Depression)

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS,** and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking *Actiq* (see **ADVERSE REACTIONS** - Post-Marketing Experience). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

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

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

Disposal of Used *Actiq* Units

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

1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened *Actiq* Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

1) Remove the *Actiq* unit from its blister package using scissors, and hold the *Actiq* by its handle over the toilet bowl.
2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3) Dispose of the handle in a place that is out of the reach of children.
4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, blister packages, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

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

Laboratory Tests

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

Drug Interactions

See **WARNINGS**.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy - Category C

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Actiq is not indicated for use in labor and delivery.

Nursing Mothers

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

Pediatric Use

See WARNINGS.

Geriatric Use

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

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

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

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

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

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

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

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

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of *Actiq* that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.

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

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

The following adverse events not reflected in Table 3 occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 4 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse events are listed in descending order of frequency within each body system.

Table 4.

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

Dose Group	200-600 mcg	800-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	98	83	53	27	152
Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	9
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	36	25	26	45
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anxiety	9	8	8	7	15
Somnolence	8	13	9	7	15
Confusion	2	6	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	8	4	3
Stupor	4	1	0	0	3
Vasodilatation	3	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	4	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

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

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to *Actiq*.

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

OVERDOSAGE

Clinical Presentation

The manifestations of *Actiq* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

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

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

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

Treatment of Overdose in Opioid-Tolerant Patients

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

General Considerations for Overdose

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

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

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

DOSAGE AND ADMINISTRATION

***Actiq* is contraindicated in non-opioid tolerant individuals.**

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

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

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

Administration of *Actiq*

The blister package should be opened with scissors immediately prior to product use. The patient should place the *Actiq* unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The *Actiq* unit should be sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The *Actiq* unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in *Actiq* clinical trials. If signs of excessive opioid effects appear before the unit is consumed, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

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

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

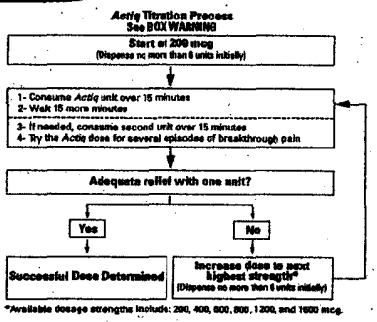
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



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

Dosage Adjustment

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

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

Discontinuation of *Actiq*

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

SAFETY AND HANDLING

Actiq is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see **BOX WARNING, WARNINGS, PRECAUTIONS** and **PATIENT LEAFLET**).

Store at 20-25°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.)

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

DISPOSAL OF ACTIQ

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

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

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

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

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

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

℞ only.

DEA order form required. A Schedule CII narcotic.

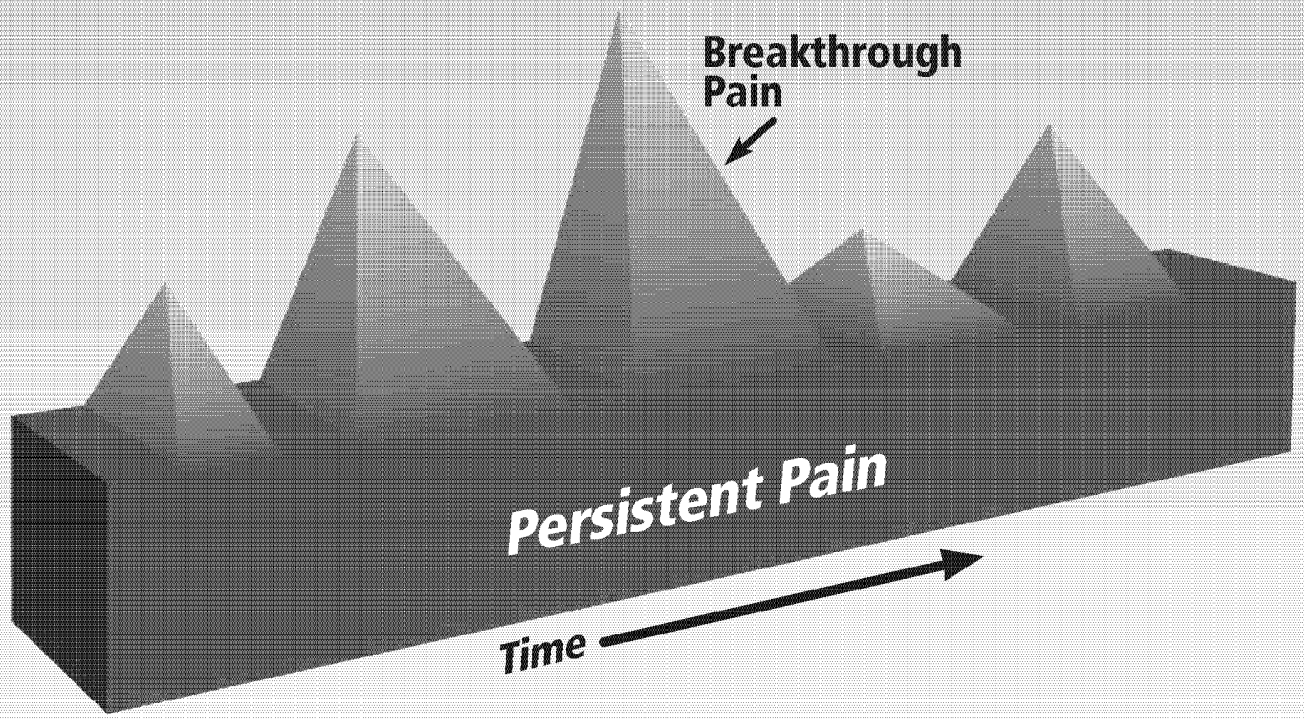
Manufactured by:
Cephalon, Inc., Salt Lake City, UT 84116, USA

U.S. Patent Nos. 4,671,953; 4,863,737; and 5,785,989
Printed in USA

#1598.02

BREAKTHROUGH CANCER PAIN

A clinical entity in need of treatment



Breakthrough cancer pain – BTCP – is a transitory flare of pain in patients otherwise controlled with chronic opioid therapy.[1]

Actiq®

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

Please see a Cephalon representative for full prescribing information, including boxed warning. For more information, please call Cephalon Professional Services at 1-800-896-5855.

Reference: 1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain.* 1990;41:273-281.

ACT249

41 (1990) 273–281

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Breakthrough pain: definition, prevalence and characteristics

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Summary In the cancer population, the term breakthrough pain typically refers to a transitory flare of pain in the setting of chronic pain managed with opioid drugs. The prevalence and characteristics of this phenomenon have not been defined, and its impact on patient care is unknown. We developed operational definitions for breakthrough pain and its major characteristics, and applied these in a prospective survey of patients with cancer pain. Data were collected during a 3 month period from consecutive patients who reported moderate pain or less for more than 12 h daily and stable opioid dosing for a minimum of 2 consecutive days. Of 63 patients surveyed, 41 (64%) reported breakthrough pain, transient flares of severe or excruciating pain. Fifty-one different pains were described (median 4 pains/day; range 1–3600). Pain characteristics were extremely varied. Twenty-two (43%) pains were paroxysmal in onset; the remainder were more gradual. The duration varied from seconds to hours (median/range: 30 min/1–240 min), and 21 (41%) were both paroxysmal and brief (lancinating pain). Fifteen (29%) of the pains were related to the fixed opioid dose, occurring solely at the end of the dosing interval. Twenty-eight (55%) of the pains were precipitated; of these, 22 were caused by an action of the patient (incident pain), and 6 were associated with a non-volitional precipitant, such as flatulence. The pathophysiology of the pain was believed to be somatic in 17 (33%), visceral in 10 (20%), neuropathic in 14 (27%), and mixed in 10 (20%). Pain was related to the tumor in 42 (82%), the effects of therapy in 7 (14%), and neither in 2 (4%). Diverse interventions were employed to manage these pains, with variable efficacy. These data clarify the spectrum of breakthrough pains and indicate their importance in cancer pain management.

Key words: Cancer pain; Breakthrough pain; Opioids; Pain management

Introduction

The term, breakthrough pain, has become accepted in the lexicon of the cancer pain specialist and refers generally to a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy. In the population of cancer pain patients, breakthrough pain is frequently mentioned as a clinical problem, and supplemental opioid doses are often suggested to manage it when it occurs [6,10,17]. Access to these supplemental, or 'rescue,' doses of an opioid during chronic opioid therapy is now commonly recommended [10], and this can be taken as further evidence of the clinical recognition that transient pains often complicate the efficacy of analgesic therapy in cancer patients.

Given this recognition, it is remarkable to note that the phenomenon of breakthrough pain has never been assessed empirically. Although it is evident that transient pains have protean characteristics, their prevalence and specific features have not been evaluated. The relationship of these

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pains to factors associated with the patient, the neoplasm or anti-neoplastic therapies is unknown, and the efficacy of therapeutic interventions has never been determined. In short, despite clinical experience indicating that transient pains are a common and often difficult problem, an acceptable definition for breakthrough pain is lacking and the phenomenology described by this term is obscure.

Methods

To determine the prevalence and characteristics of breakthrough pain, a brief questionnaire was developed and used in a prospective survey of cancer pain patients. Pilot data from this survey have been reported previously [12].

Survey instrument

Given the paucity of information about transitory pains in cancer patients, and the likelihood that the clinical use of the term 'breakthrough pain' encompasses a diverse group of painful experiences, a broad definition was applied in this survey. Although it was recognized that most patients would be receiving opioids, it was decided a priori that opioid use was not a reasonable criterion for the definition of these pains. Rather, worsening of pain intensity and a temporal profile characterized by transience were the key criteria in this operational definition, as follows:

Breakthrough pain was defined as a transitory increase in pain to greater than moderate intensity (that is, to an intensity of 'severe' or 'excruciating'), which occurred on a baseline pain of moderate intensity or less (that is, no pain or pain of 'mild' or 'moderate' intensity). *Baseline pain* was defined as that reported by the patient as the average pain intensity experienced for 12 or more hours during the 24 h prior to the interview. Patients whose baseline pain was severe or worse were said to have uncontrolled pain and were not assessed for breakthrough pain.

The specific features of breakthrough pain evaluated in the questionnaire were derived from principles of cancer pain assessment [10,16–18] and clinical experience (Table I). For the purposes of the survey, these characteristics were defined as follows:

Temporal characteristics. Breakthrough pains were characterized by frequency, type of onset, and duration. The onset of a breakthrough pain was defined as the time required for the pain to progress from first perception to maximal intensity; to improve reliability, this variable was dichotomized as paroxysmal (maximal in intensity within 3 min) versus gradual (longer than 3 min). Duration, as recalled by the patient, was recorded in minutes.

Pain severity. Pain severity was assessed using a 5-point categorical scale ('none,' 'slight,' 'moderate,' 'severe,' and 'excruciating'). By definition, all breakthrough pains had been rated by the patient as either severe or excruciating.

Pain location. The location of the breakthrough pain was noted and compared to the location of the baseline pain.

TABLE I

CHARACTERISTICS OF BREAKTHROUGH PAINS

Pain severity
Pain location
Temporal characteristics
Frequency
Onset
Duration
Relationship to fixed analgesic dose
Precipitating event
None (spontaneous)
Incident
Non-volitional precipitants
Predictability *
Pathophysiology
Somatic
Visceral
Neuropathic
Mixed
Etiology
Related to neoplasm
Related to treatment
Unrelated to neoplasm or treatment
Palliative factors

* Not assessed in this survey.

Relationship to the regularly scheduled analgesic. Although opioid use was not included in the definition of breakthrough pain, most patients were receiving regular doses of these drugs. Patients were assessed for a relationship between the analgesic regimen and transitory pains by noting whether pains occurred or markedly worsened at the end of a dosing interval.

Precipitating events. Each breakthrough pain was characterized as spontaneous, occurring without an identifiable precipitating event, or precipitated. Precipitated pains induced by an action of the patient, such as movement, swallowing, micturition, defecation or cough (commonly known as 'incident pains') were distinguished from those in which the precipitant was non-volitional.

Pathophysiology. The underlying mechanism for the breakthrough was characterized as somatic, visceral or neuropathic [2,5,6,10,15,18], as follows: Somatic pains were related to an etiology that involved somatic structures, such as bone or muscle, and were described, at least in part, as aching, stabbing or throbbing. Visceral pains were related to a lesion in a hollow or solid viscus and were described, at least in part, as diffuse, gnawing or crampy if hollow viscus was involved, or aching or sharp if a solid viscus was involved. Neuropathic pains were related to a lesion involving peripheral or central afferent neural pathways and were described, at least in part, as unfamiliar, burning or lancinating. The pathophysiology was labeled mixed if these criteria were not met or multiple concurrent processes were observed.

Etiology. Etiologies were grouped into those related to the neoplastic lesion, to an anti-neoplastic therapy, or to neither the cancer nor its treatment.

Palliative factors. Patients were asked to describe the specific factors they believed to be responsible for the cessation of the transient flare of pain.

Survey methodology

All adult inpatients consecutively referred for evaluation and treatment by the Pain Service at Memorial Sloan-Kettering Cancer Center during a 3 month period were considered to be candidates for the survey. All patients were evaluated by one of the authors (NH). Consistent with the standard approach to these patients, the clinical evaluation was usually followed by administration of an analgesic drug or adjustment of the current dose of the analgesic in use. Daily evaluation resulted in dosage increments in most patients following the initial consultation.

Patients who achieved relatively stable doses (defined as less than 20% increase in opioid dose per day) for 2 consecutive days were queried about breakthrough pain. Patients were first asked whether or not they would endorse the statement that, on average, pain was absent, mild or moderate for more than 12 h during the prior 24 h. Patients who answered negatively to this question were considered to have uncontrolled pain and were not evaluated further. Patients who agreed, however, were then asked whether or not they had experienced temporary flares of severe or excruciating pain during this period. Patients who responded affirmatively to the latter question were considered to have breakthrough pain and were administered the remainder of the pain-related questions. In addition, demographic data, analgesic history and information about disease status and anti-neoplastic therapies were also collected from all patients.

Group comparisons were performed using chi-square or *t* tests.

Results

Ninety patients were evaluated during this 3 month period. Seventy achieved the initial criterion of stable opioid dosing for 2 or more days. Sixty-three (90%) of these patients reported pain of moderate intensity or less for greater than 12 h/day during the day prior to the interview. Of these patients with stable opioid dose and moderate pain or less, 41 (63%) described one or more breakthrough pains during the preceding 24 h. Specifically, 32 noted 1 type of breakthrough pain, 8 identified 2 distinct types, and 1 reported 3 types. Thus, these 41 patients represented 51 breakthrough pain syndromes.

Demographics, analgesic consumption and tumor-related information about these patients is

TABLE II

NUMBER (%) OF PATIENTS WITH BREAKTHROUGH PAINS AND SPECIFIC DEMOGRAPHIC, ANALGESIC AND ONCOLOGIC CHARACTERISTICS

N = 41 patients

Age: Median: 51 years Range: 15–81 years	
Sex: Male 19 Female 22	
Tumor diagnosis	
Genitourinary	11
Head/neck	5
Gastrointestinal	4
Lung	3
Sarcoma	3
Unknown primary	3
Breast	2
Melanoma	2
Other	8
Extent of disease	
Remission	3
Local extension	1
Metastatic	37
Opioid consumption during the previous 24 h (in intramuscular morphine equivalent milligrams *)	
1–20	9
21–40	9
41–60	5
61–80	2
81–100	2
>100	10
No opioids	4

* Based on standard relative potency tables, using an oral : intramuscular conversion for morphine of 3 : 1.

described in Table II. There were no significant differences between those patients fulfilling the criteria for breakthrough pain and those without this phenomenon on any of these characteristics.

The number of breakthrough pain episodes during the 24 h period varied widely among patients. The median number of breakthrough pains was 4 (range 1–3600 pains). Fifteen patients described 1–3 painful episodes, 14 noted 4–6 pains, 7 reported 7–10 pains, and 5 patients had more than 10 breakthrough pains during the prior day. The maximum number was reported by a patient with lung cancer who experienced a brief and stabbing somatic pain in the region of a rib fracture that occurred with a paroxysm of cough every minute.

An onset within 3 min was described in 22 (43%) of the 51 pains; the remainder required longer to reach maximal intensity. The median duration of the pains was 30 min (range 1–240 min), including 21 pains reported to persist for 20 min or less. Twenty-one (41%) pains were characterized by both rapid onset and brief duration.

As noted, severity was one of the criteria used to define breakthrough pain. All breakthrough pains, therefore, were severe or excruciating in intensity, and these data cannot be used to clarify the range of pain intensity that characterizes transient pains in cancer patients.

All patients with breakthrough pain also experienced at least one continuous pain, which in most cases was managed in part with a fixed dose opioid regimen. The location of these persistent pains varied widely among patients. Breakthrough pains usually, but not always, occurred in the same location. Specifically, 49 (96%) of the breakthrough pains were propinquitous to a more continuous pain, whereas 2 (4%) were reported to be an entirely new site of pain. Most cases of breakthrough pain therefore represented a transient exacerbation of a pain already experienced.

Pain onset or a marked worsening of the pain occurred at the end of the dosing interval of the regularly scheduled analgesic in 15 (29%) pains (14 patients). The scheduled analgesic in all but 4 patients was an opioid. These breakthrough pains were not significantly different from pains unrelated to the analgesic regimen in frequency, type of onset, duration, prevalence of specific precipitants, pathophysiology or etiology.

Each breakthrough pain was characterized, if possible, by the precipitant that preceded it (Table III). Precipitants were identified prior to 28 (55%) pains. Most of these precipitating events were volitional, and the resultant breakthrough pain can thus be termed an 'incident' pain. Some of the pains that were related to the analgesic regimen were also characterized by other specific precipitants. Six (12%) pains could be attributed to both end of dose failure and a specific precipitant; 9 (18%) were characterized by a relationship to the dose alone, and 22 (43%) had a precipitant unre-

TABLE III

PRECIPITATING EVENTS FOR BREAKTHROUGH PAIN

N = 51 pains.

No identified precipitant	23
Precipitants	28
Volitional (incident)	
Movement in bed	7
Walking	4
Cough	6
Sitting	2
Standing	2
Touch	1
Non-volitional	
Bowel distension	4
Ureter/renal pelvis distension	1
Medication regurgitated *	1

* Pain flare following regurgitation of a single dose of opioid drug.

lated to the analgesic dose. The remainder of the pains (14 pains or 27% of the total sample) were completely idiopathic.

Seventeen (33%) pains were somatic, 10 (20%) were visceral, 14 (27%) were neuropathic, and 10 (20%) were mixed. There were no significant differences in any of the demographic or pain-related variables among the pathophysiologies, but the sample size in this survey was insufficient to validly assess these relationships. Of note, there was no relationship between the pathophysiology and rapid onset of the pain, as defined previously. Of 22 pains with rapid onset, 9 (41%) were somatic, 3 (14%) visceral, 6 (27%) neuropathic and 4 (18%) mixed.

Thirty-nine (76%) breakthrough pain syndromes were specifically related to a known neoplastic lesion. Ten (20%) could be attributed to an effect of an anti-neoplastic therapy, and 2 (4%) were unrelated to either the cancer or its treatment. Again, the sample size was too small to allow valid group comparisons, and relationships between the etiology of breakthrough pain and other variables remain conjectural.

Most patients could identify specific interventions that either aborted the pain or reduced the frequency or intensity of subsequent pains (Table IV). Importantly, many of these palliative factors were not provided by the medical staff, but were rather discovered by the patient through trial and error to be useful in mitigating or forestalling the pain.

TABLE IV

PALLIATIVE FACTORS REPORTED BY PATIENTS TO BE USEFUL IN ALLEVIATING A BREAKTHROUGH PAIN OR REDUCING ITS FREQUENCY OR INTENSITY

Some patients had more than one palliative factor.

Use of rescue dose	16
Change in position or movement	13
Use of rescue dose and change in position	2
Use of regularly scheduled dose	6
Miscellaneous	9
Defecation	2
Flatus	1
Suppressed cough	3
Antacid	1
Sleep	1
Squeeze painful region	1
No intervention known to the patient	5

Discussion

This survey is the first devoted to the cancer pain phenomenon generally known as breakthrough pain. It was undertaken to highlight this clinical problem in cancer pain management, define it explicitly as a point of departure for future investigations, and begin to clarify its prevalence and characteristics.

Several important criticisms of the present survey are possible. These may limit the generalizability of some of the data and must be addressed in future studies of breakthrough pain. First, the study population was referred to a Pain Service at a large cancer hospital and was therefore unquestionably selected for difficult pain problems. The prevalence of transient pains determined in this survey may therefore be higher than other groups of cancer pain patients. Second, the operational definitions employed in this survey, while clearly more precise than current descriptions in the clinical literature [1–4,9,10], may also introduce bias. For example, the decision to exclude opioid use from the definition of breakthrough pain could

potentially exaggerate the prevalence by labeling as breakthrough pain some painful experiences that most practitioners would exclude. Third, there has been no independent validation of the survey instrument. Indeed, several of the factors assessed, such as pain pathophysiology, are themselves constructs in need of validation. Finally, there was a potential for observer bias in using one of the treating clinicians as the interviewer, as well as bias in relying on patient recall for events during the preceding 24 h. Additional studies of breakthrough pain are needed to replicate the findings of this survey in different populations and address these potential methodological problems.

Prevalence and characteristics of breakthrough pains

Transient pains were extremely prevalent in this population of cancer patients referred for pain management. Not surprisingly, the characteristics of these pains were highly diverse. The proximate cause could be related to an insufficient amount of analgesic drug, a specific precipitant, or both; less than one-third were fully idiopathic. Other features, including the temporal profile, location, pathophysiology and type of underlying etiology, were similarly variable.

This variability in breakthrough pain syndromes was such that no substantial group differences could be discerned. Although surveys with larger samples may yet discover relationships between specific characteristics of breakthrough pain and demographic or clinical features of the patient, the data available suggest that, unlike syndromes associated with more persistent cancer pain [11], breakthrough pains cannot be characterized in a manner that yields broad implications for lesion recognition, pain pathogenesis or prognosis.

Among the most important characteristics of these transient pains is the relationship to the baseline analgesic regimen. The present survey inferred a relationship between the analgesic dose and breakthrough pain from the phenomenon of end-of-dose onset or exacerbation of pain. Although this is reasonable, it must be noted that better evidence would be provided by the observation that these pains improve with an increase in dose or a shortening of the dosing interval, maneuvers that this survey was not designed to assess. Nonetheless, it can be postulated that some breakthrough pains are related to baseline opioid dose, and that this may be true even when a change at the end of the dosing interval cannot be demonstrated (e.g., with continuous infusion techniques). This does not negate the common observation that incident pains, which are herein considered to be a subtype of breakthrough pain, tend to respond less well to opioids than continuous pains [13], but does contradict the conclusion that these pains are intrinsically resistant to opioid treatment.

Breakthrough pains with rapid onset also comprise an important subgroup. The present survey defined this characteristic as maximal pain intensity within 3 min. This criterion was employed despite the possibility that it could obscure the prevalence of specific pain patterns that may have unique clinical features. The broader definition, however, recognized the difficulties expressed by patients in recalling this characteristic reliably and was more likely to capture the spectrum of rapid onset breakthrough pains. It was anticipated that neuropathic mechanisms would be overrepresented among pains of rapid onset and brief duration. Such neuropathic pains are important to identify since there is clinical evidence that they may be particularly responsive to specific drugs, such as some anticonvulsants [14]. Surprisingly, this survey demonstrated that somatic and visceral pathophysiologies were as common in pains of this type as neuropathic mechanisms. Although it remains possible that some types of brief pains, such as those with maximal intensity at onset, may indeed be typical of a neuropathic mechanism, these results indicate that brief pains with rapid onset may have variable mechanisms and suggest the need for careful assessment in the clinical setting.

The great variety of precipitating events was another important finding of this survey. Contrary to assumptions that appear in the clinical literature, some precipitating events clearly identified by the patient were not under voluntary control and did not, therefore, conform to the usual definition of incident pain. Recognition of these nonvolitional precipitants is important, since they,

like those under voluntary control, may be amenable to treatment.

The identification of precipitants relates closely to a facet of breakthrough pain, predictability, that was not assessed in the present survey. Predictability of pain appeared to be a salient characteristic in these patients, influencing the distress caused by the pain and the options available for therapy. It is likely that there is an association between the predictability of the pain and both the type and reliability of the precipitant. This feature should be assessed in future surveys of breakthrough pain.

These data also suggest that breakthrough pains can be usefully distinguished by presumed pathophysiology and etiology. These constructs are commonly employed by clinicians to select adjunctive therapies (e.g., non-steroidal anti-inflammatory drugs for bone pain) and determine prognosis. Similarly, they appear to be useful in selecting a treatment approach for the breakthrough pain.

Patients reported benefit from a great variety of interventions for breakthrough pain. Some were offered by the medical staff, but many, such as changes in position, were discovered fortuitously by the patient. Given the likelihood that many of the pains remit spontaneously after a short time, it is probable that some patients attributed benefit to interventions that actually had little impact. Future investigations will also need to clarify these therapeutic considerations more systematically.

An approach to the management of breakthrough pain

Many published guidelines for the therapy of cancer pain [1,6,7,10,16,17] allude to the problem of transient exacerbation of pain, but none describes the management of this problem beyond the use of supplemental doses of an opioid. The experience detailed in this survey indicates that a more comprehensive approach is needed.

Four principles can be proposed to guide the management of breakthrough pain. First, the variability observed in this survey indicates the importance of a comprehensive assessment in the clinical approach to these pains. This evaluation should determine pain characteristics, etiology and pathophysiology, and the relationship of the pain to the patient's overall clinical status.

Second, consideration should be given to primary treatment of the underlying etiology. Primary treatments include a variety of approaches, such as radiotherapy to a painful lesion, surgical repair of a fractured bone, decompression of obstructed bowel, and administration of antibiotics for a localized infection. The feasibility, risks and potential benefits of these treatments vary from patient to patient, and the successful implementation of any requires careful assessment and appropriate patient selection.

Third, given the relationship between the occurrence of breakthrough pains and baseline analgesic (usually opioid) regimen, adjustments in the dose of the regularly scheduled analgesic should be considered in every case. Specifically, the dose of this opioid should be increased until either favorable effects occur or intolerable and unmanageable side effects supervene. In this situation, limiting side effects typically occur during the intervals between the severe pains [7].

Finally, primary analgesic approaches directed specifically at the breakthrough pain must be considered. Clinical experience indicates that the most important approach entails the use of an opioid 'rescue dose,' a supplemental 'as needed' dose offered concurrently with the regularly scheduled drug. Although neither the pharmacokinetics nor the pharmacodynamics of the 'rescue dose' has been studied, an opioid with a short half-life and rapid onset of action can be recommended empirically; if the regularly scheduled opioid has a short half-life, this drug can also be selected as the 'rescue.' Although management is simplified if the same route of administration is used for both the 'rescue' and the fixed dose, occasional patients on oral dosing find that the onset of action of an oral dose is too slow and have better results with a parenteral 'rescue.' The recent advent of patient-controlled analgesia systems in devices capable of delivering continuous infusion, particularly ambulatory infusion pumps for continuous subcutaneous infusion, can, if available, expedite the administration of supplemental doses in those receiving opioid infusions.

The dose of an opioid 'rescue' must reflect the

level of the baseline dose. Some clinicians begin with a dose roughly equivalent to 5–10% of the total daily opioid intake administered every 2–3 h as needed. However, the size of the most effective dose that does not produce intolerable side effects is unknown in any individual case, and titration of the 'rescue dose' should be viewed as a key principle in the management of breakthrough pain by this approach.

Other pharmacological approaches may be useful in some types of breakthrough pain. As noted, there is substantial evidence that patients with lancinating neuropathic breakthrough pains may respond to an adjuvant analgesic, such as an antidepressant or anticonvulsant [10,14]. Some patients with breakthrough pain related to neoplastic invasion of bone or nerve trunk appear to benefit, at least temporarily, from the administration of a corticosteroid. The use of specific drugs to reduce the frequency of precipitating events, such as antitussives, laxatives, antiperistaltic drugs or agents that may reduce muscle spasm, may also be effective.

Non-pharmacologic approaches should also be considered. Physiatric techniques, such as physical therapy or the use of orthotics, may ameliorate the musculoskeletal complications that predispose to breakthrough pains; bracing of the painful part may be very useful in patients with severe movement-related pain. Some patients appear to benefit from psychological techniques [4], such as distraction. Anesthetic approaches that are commonly used in the treatment of chronic cancer pain are sometimes beneficial in those with breakthrough pain; in particular, some patients clearly benefit from chemical neurolysis, the purpose of which is to deafferent the painful part [8]. Continuous epidural local anesthetic infusion is a new anesthetic technique that obviates some of the risks involved in neurolysis and may prove to be very useful in the treatment of breakthrough pain [1,9]. Finally, surgical deafferentation of the painful part, by cordotomy for example, can also be considered in selected patients with refractory breakthrough pain. There is evidence that patients with a peripheral nociceptive lesion are more likely to respond to such procedures than those with a painful neuropathic lesion associated with deafferentation [15].

This survey demonstrates that transient pains in cancer patients are common and diverse in presentation. The clinical literature on cancer pain does little to illuminate the manifestations or impact of these pains and, indeed, may have obscured the variability of these phenomena. Additional surveys are needed to categorize these pains and relate their clinical presentation to underlying etiology and pathogenesis. Studies of treatments for breakthrough pains, such as the 'rescue dose,' are clearly needed.

Acknowledgement

The authors would like to thank Dr. Kathleen Foley for her critical review of the manuscript.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Tracie A. Parker
Senior Manager
Regulatory Affairs
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

RE: NDA # 20-747
Actiq® (oral transmucosal fentanyl citrate)
MACMIS ID # 12800

Dear Ms. Parker:

This letter responds to Cephalon, Inc's (Cephalon) submission dated October 21, 2004 requesting comments on proposed promotional materials for Actiq® (oral transmucosal fentanyl citrate). The Division of Drug Marketing, Advertising, and Communications (DDMAC) provides comments on the following proposed promotional materials:

- Actiq Spanish Warning Stickers (ACT224)
- Actiq Montage Journal Ad (ACT217)
- Actiq Detail Aid (203)

Since many claims and representations are similar or closely related, DDMAC's comments on a particular claim or representation apply to similar claims or representations in these and future promotional materials for Actiq.

Actiq Spanish Warning Stickers

We have reviewed the Actiq Spanish Warning Stickers and have no comments at this time.

Actiq Montage Journal Ad

Misleading Presentation of Information

You present the claim, "Patients can use ACTIQ anywhere, as soon as they begin to feel breakthrough cancer pain." This claim is misleading because it implies that it is appropriate for patients to consume as many Actiq units as needed to control all episodes of breakthrough cancer pain per day, when such is not the case. The PI specifically states, "Once a successful dose has been found..., patients should limit consumption to four or fewer units per day." Therefore, DDMAC recommends including adequate and prominent

context to avoid this misleading implication. We refer to our comment letters dated January 26, 1999 and September 9, 2004 regarding similar claims.

Overstatement of Efficacy

You present the claims, "When onset matters...ACTIQ® **responds**" and "**Relief** at hand" (emphasis added). These claims overstate the efficacy of Actiq because they imply that Actiq is guaranteed to provide adequate and effective response and pain relief for every patient every time the product is used, when such is not the case. We note that in your cover letter, you state, "...the tag line ["Relief at hand"] is balanced with "With ACTIQ, pain relief may be observed in 15 minutes. Patients may experience pain relief..." However, we remind Cephalon that misleading claims can not be corrected by true information relating to risk or efficacy. We refer to our comment letter dated January 26, 1999 regarding a similar issue.

You present the claim "Patients may experience relief while taking ACTIQ..." This claim is misleading because it implies that onset of action will occur at any time period following commencement of administration, which is inconsistent with the PI. The PI specifically states, "Actiq produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration." We refer to our comment letter dated June 17, 2004 regarding this similar claim.

Minimization of Risk

You present the claim, "The adverse events seen with ACTIQ are typical opioid side effects,..." This claim is misleading because Actiq is the only opioid approved with a risk management plan, and there are several prominent boxed warnings related to safety that appear in the approved labeling and that are exclusive to Actiq. Therefore, statements implying that the safety profile of Actiq is similar to other opioids are considered misleading because this presentation implies that Actiq is as safe as other opioids, when such has not been demonstrated by substantial evidence or substantial clinical experience. We refer to our comment letters dated January 26, 1999, February 24, 1999 and August 29, 2002 regarding this issue.

You present the header "Safety" prior to the section describing adverse events associated with Actiq. This heading is misleading because it frames this section to suggest that the information presented is related to Actiq safety (i.e., Actiq has been shown to be safe), when, in fact, this section discusses important risk information. Therefore, we recommend that you revise this header to clarify that important risk information is presented (i.e., "Risk Information").

Actiq Detail Aid

The above comments should also be applied to this proposed promotional piece. In addition, DDMAC has the following comments:

Risk Management Plan

According to section 5.3 of the Actiq Risk Management Plan (RMP), "Detail aids for Actiq will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all leave behind detail aids will also prominently display the detail flag." DDMAC recommends ensuring that this proposed detail aid is compliant with the RMP.

Omission of Important Risk Information

According to section 5.3 of the Actiq Risk Management Plan (RMP), "Detail aids for Actiq will emphasize the three key safety messages," which consists of Child Safety Messages, Proper Patient Selection Messages, and Prevention of Diversion and Abuse Messages. This detail aid is misleading because you fail to communicate any Prevention of Diversion and Abuse Messages.

Overstatement of Efficacy

You present the claim, "Duration of pain relief was found to be 1 hour (the last time measured) following completion of the ACTIQ unit." This claim is misleading because it implies that duration of pain relief of one hour following completion of the Actiq unit has been evaluated and all patients who use Actiq will have pain relief for one hour, when such has not been demonstrated by substantial evidence. The PI specifically states, "Actiq produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes **following administration**" (emphasis added). Therefore, claims of efficacy beyond 45 minutes after completion of the Actiq unit are inconsistent with the PI.

You present the claim, "Dosing and titrating to optimize **control**" (emphasis added). This claim of "control" is misleading because it implies that all patients will experience control of their breakthrough cancer pain with Actiq, which thereby overstates the efficacy of Actiq. We refer to our comment letter dated August 29, 2002 and September 9, 2004 regarding a similar issue.

General

You present the claim, "Highly lipophilic for rapid absorption across the oral mucosa with slower absorption from the GI tract." For consistency and completeness with the PI, we suggest that you clarify that it is the oral transmucosal dosage form that has these absorption characteristics.

You present the claim, "Patients started on 200 mcg titrated to a mean maintenance dose of 789 mcg" and "86% of patients were titrated to 400 mcg or higher." For consistency and completeness with the PI, we suggest that you also include the material fact, "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."

We refer to your cover letter where you request approval to modify the detail aid for future printings to change the number in "over 48 million units of ACTIQ have been prescribed"

without submission 30 days prior to dissemination. Approval is **not** granted as such claims are promotional and require verification.

If you have any questions, please contact me by facsimile (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 12800 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Jialynn Wang, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Jialynn Wang
11/24/04 02:53:03 PM

TOTAL P.06

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Tracie A. Parker
Senior Manager
Regulatory Affairs
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380-4245

RE: NDA # 20-747
Actiq® (oral transmucosal fentanyl citrate)
MACMIS ID # 12674

Dear Ms. Parker:

This letter responds to Cephalon, Inc's (Cephalon) submission dated August 26, 2004 requesting comments on proposed promotional material for Actiq® (oral transmucosal fentanyl citrate). The Division of Drug Marketing, Advertising, and Communications (DDMAC) provides comments on the following proposed promotional material:

- Actiq Patient Profiles (ACT 208)

Since many claims and representations are similar or closely related, DDMAC's comments on a particular claim or representation apply to similar claims or representations in these and future promotional materials for Actiq.

Unsubstantiated Comparative Claims

You present multiple claims under the header, "Managing breakthrough pain," such as, "Prior treatment: Ibuprofen and Percocet" and "Prior treatment: MSIR®" in addition to claims that compare Actiq with "regular rescue medication." Such claims are misleading because they imply that there are other agents approved for the same indication as Actiq, when such is not the case. Therefore, DDMAC recommends deletion of any claims that make this misleading implication. We refer to our comments dated June 17, 2004 where we addressed this specific issue.

Lack of Important Contextual Information

You present claims such as, "'Now, if the pain breaks through an interrupts my homework, I use ACTIQ to help manage it'," "'At school, when I felt the pain coming on, I'd excuse myself to take an ACTIQ,'" and "Frequency: 5-6 breakthrough pain episodes per day." These and similar claims are misleading because they imply that it is appropriate for patients to consume

as many Actiq units as needed to control all episodes of breakthrough cancer pain per day, when such is not the case. The PI specifically states, "Once a successful dose has been found..., patients should limit consumption to four or fewer units per day." Therefore, DDMAC recommends including adequate and prominent context to avoid this misleading implication. We refer to our comment letter dated January 26, 1999 regarding a similar claim.

Misleading Presentation of Information

Throughout this proposed promotional piece, you present multiple claims based upon patient reported outcomes. For example, you present claims such as, "Pain used to ruin my appetite...until I started ACTIQ," "Uncontrolled pain deepened depression and anxiety," and "ACTIQ works...especially at night. It relieves the pain enough for me to go to sleep." These and other claims are misleading because they overstate the efficacy of Actiq by implying that Actiq has a positive impact on physical, role, and mental functioning, sleep, appetite, general health perception, and psychological well-being. Such claims need to be substantiated with adequate and well-controlled clinical trials using well-developed and validated instruments to assess the effects of Actiq treatment on physical, role, and mental functioning, sleep, appetite, general health perception, and psychological well-being.

You present the claim, "Regardless of pain pathophysiology, patients in clinical studies titrated to the same mean dose of 600 mcg." This claim is misleading because it implies that patients in all clinical studies titrated to a mean dose of 600 mcg, which is inconsistent with the PI. The PI specifically states that in a double-blind placebo controlled crossover study, patients were titrated to a mean Actiq dose of 789 ± 468 mcg.

You present the claim "Within 15 minutes of starting medication, patients using ACTIQ rated their pain relief at 67%...." This claim is misleading because it implies that onset of action will occur at any time period following commencement of administration, which is inconsistent with the PI. We refer to our comment letter dated March 4, 2004 regarding a similar claim.

Overstatement of Efficacy

You present the claim, "Portability, convenience and control." This claim of "control" is misleading because it implies that all patients will experience control of their breakthrough cancer pain with Actiq, which thereby overstates the efficacy of Actiq. We refer to our comment letter dated August 29, 2002 regarding this issue.

If you have any questions, please contact me by facsimile (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 12674 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Jialynn Wang, Pharm.D.
LT, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jialynn Wang
9/29/04 10:33:43 AM

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Actiq® (oral transmucosal fentanyl citrate) CII

When onset matters...ACTIQ® responds.

- ACTIQ — The only fentanyl product that allows for rapid absorption across the oral mucosa with slower absorption from the GI tract[1]
- With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[2]
- Patented oral transmucosal system (OTS™)
- Both the blood profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed[3]
- Shown to be effective in patients with BTCP (patients in clinical trials included those with somatic, visceral, and neuropathic pain)[2-5]
- Risk management program dedicated to the safe and appropriate use of ACTIQ
- Over 48,000,000 units of ACTIQ have been prescribed[8]

ACTIQ oral transmucosal system (OTS™)

Please see accompanying full prescribing information, including boxed warning.

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

Actiq **is indicated only for the management of breakthrough cancer pain in patients with malignancies who are <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, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

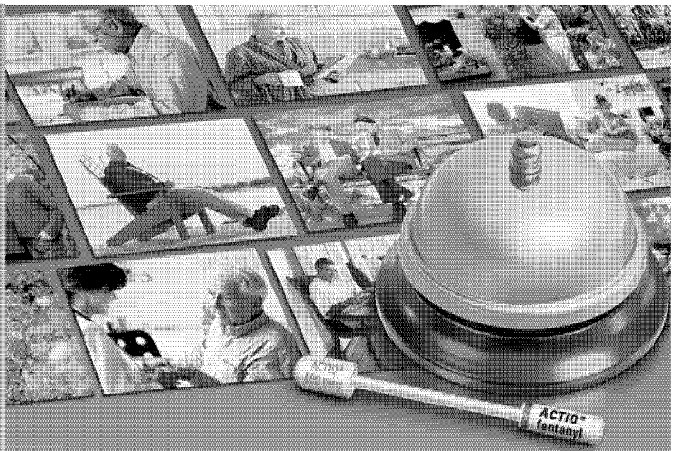
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

References: 1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain.* 1990;41:273-281. 2. ACTIQ Package Insert. Rev August 2004. 3. Streisand JB, Varvel JR, Stanski DR, et al. Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology.* 1991;75:223-229. 4. Data on file [illegible]. 5. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst.* 1998;90:611-616. 6. Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain.* 1999;79:303-312. 7. Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. *J Clin Oncol.* 1998;16:3238-3245. 8. IMS HEALTH's National Prescription Audit Plus™ April 1999-June 2004.

Cephalon



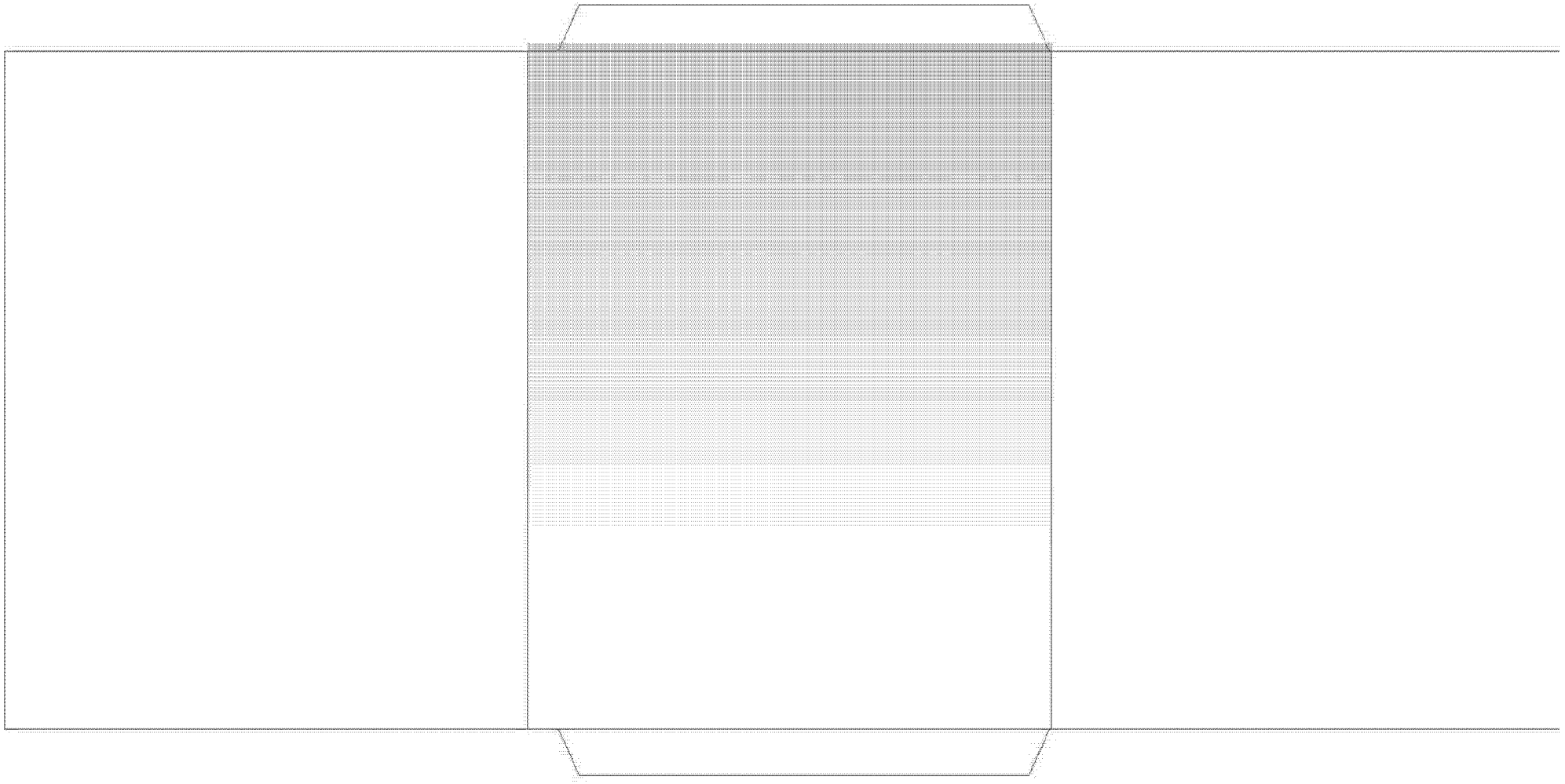
When onset matters... ACTIQ® responds.

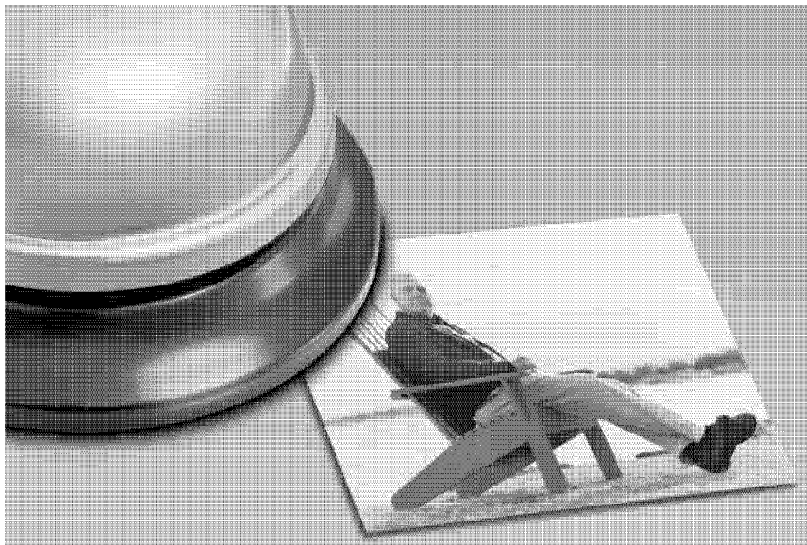
Actiq® CII

Relief at hand

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

Please see accompanying full prescribing information, including boxed warning.





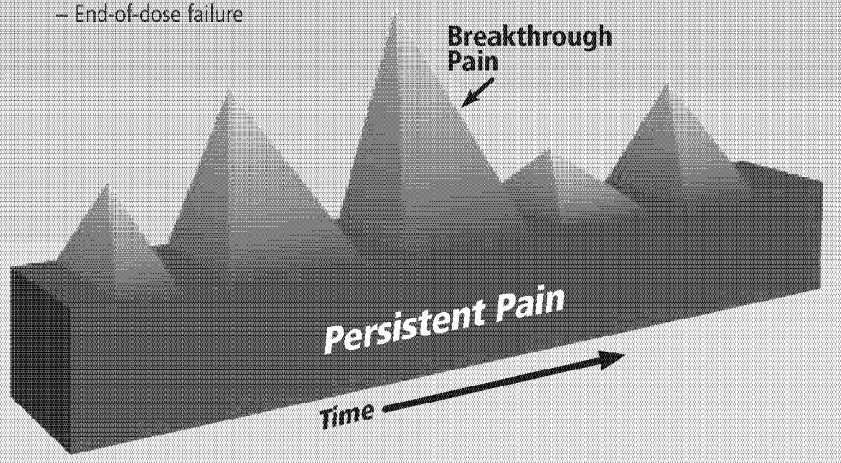
Actiq® (oral transmucosal fentanyl citrate) CII

A clinical entity in need of treatment

Breakthrough cancer pain—BTCP—is a transitory flare of pain in patients otherwise controlled with chronic opioid therapy[1]

64% of patients receiving chronic opioid therapy for cancer pain experienced BTCP in spite of controlled persistent pain (N=63). This study revealed that BTCP[1]:

- Strikes quickly and without warning in many cases
- Escalates to maximum severity in many patients in as little as 3 minutes
- Has a median duration of 30 minutes
- Occurs an average of 4 times daily in many patients
- Has 3 categories
  - Spontaneous
  - Incident/activity-related
  - End-of-dose failure



Please see accompanying full prescribing information, including boxed warning.

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

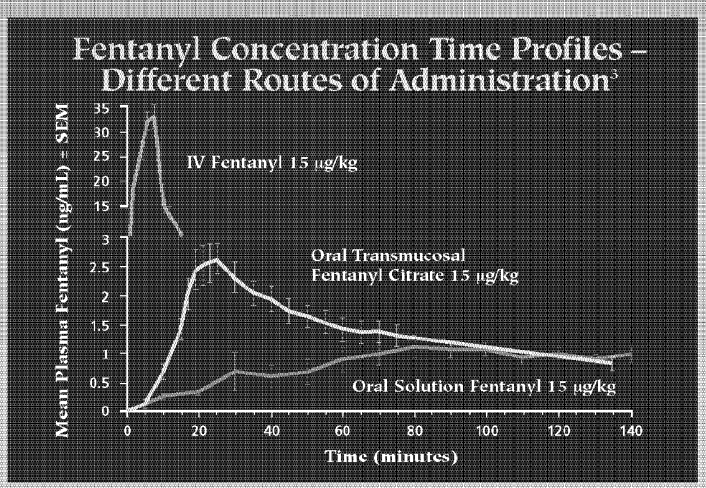
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

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

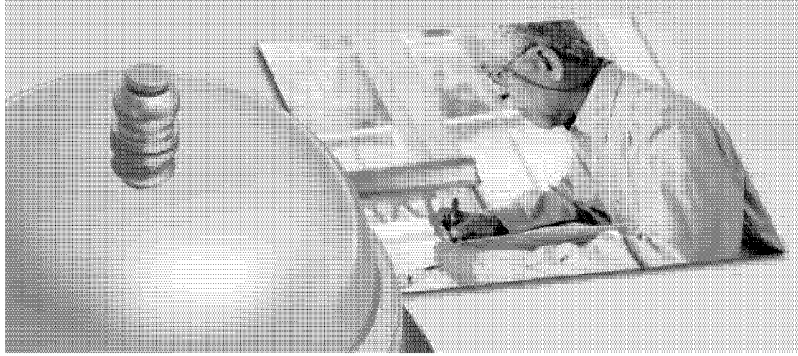
Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

A highly lipophilic opioid – fentanyl

- Highly lipophilic for rapid absorption across cell membranes[2]
- Rapid distribution into the CNS — a process with a 3- to 5-minute half-life[2]
- No pharmacologically active metabolites[2]



Adapted from Streisand, et al

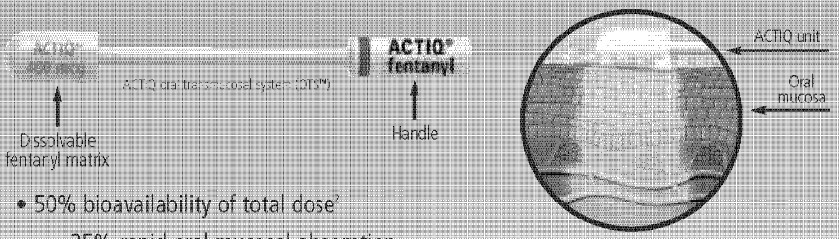


A unique delivery system – ACTIQ

Actiq® (oral transmucosal fentanyl citrate) CII

ACTIQ utilizes a patented oral transmucosal system (OTS™) designed for delivery of fentanyl

- Oral mucosa is highly permeable and well vascularized



- 50% bioavailability of total dose[2]
  - 25% rapid oral mucosal absorption
  - 25% slow GI absorption
- Both the blood profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed[2]
- 3- to 5-minute half-life for distribution into CNS[2]
- With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[2]
- The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, and dizziness[2]

Longer or shorter consumption times than the recommended 15 minutes may produce less efficacy than reported in clinical trials[2]

Please see accompanying full prescribing information, including boxed warning.

Fentanyl pharmacokinetics

- Median time to maximum plasma concentration (T_{max}) across 4 doses of ACTIQ® varies from 20-40 minutes as measured after the start of administration[1]
- Fentanyl plasma levels increase in a dose-dependent manner that is approximately proportional to the dose of ACTIQ administered[2]

Pharmacokinetics of Fentanyl

Fentanyl Dose	Median T_{max} (minutes)	C_{max} (ng/mL)	CNS Distribution $t_{1/2}$ (minutes)	Octanol:Water Partition Coefficient	Terminal Elimination $t_{1/2}$ (hours)	Bioavailability
ACTIQ 200 mcg[2]	40	0.39	3-5	816:1 at pH 7.4	3.2	50%
ACTIQ 400 mcg[2]	25	0.75	3-5	816:1 at pH 7.4	6.4	50%
ACTIQ 800 mcg[2]	25	1.55	3-5	816:1 at pH 7.4	6.4	50%
ACTIQ 1600 mcg[2]	20	2.51	3-5	816:1 at pH 7.4	6.0	50%
Oral Solution ~1200 mcg[3]	101	1.6 ± 0.6	3-5	816:1 at pH 7.4	7.8	30%
IV ~1200 mcg[2]	N/A	33.6 ± 5.5	3-5	816:1 at pH 7.4	7.1	100%

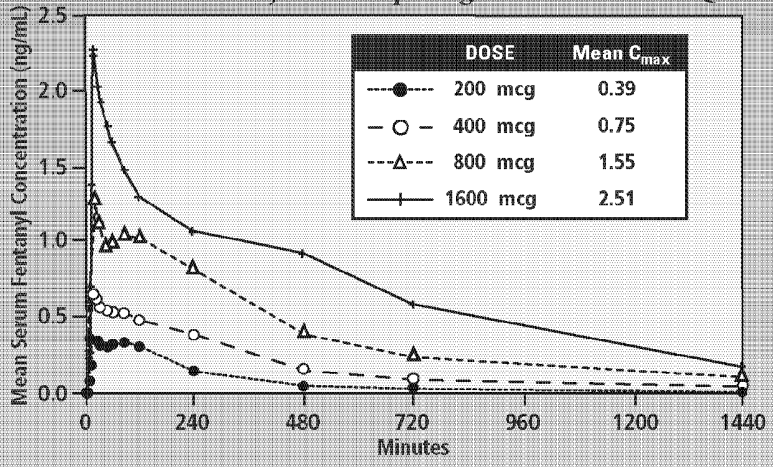
- With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[1]
- The ACTIQ unit should not be chewed or swallowed, as that might result in lower peak concentrations and bioavailability than when consumed as directed[2]
- The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, and dizziness[2]

ACTIQ dose proportionality

Actiq® (oral transmucosal fentanyl citrate)

- 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)[2]

Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of ACTIQ[2]



Please see accompanying full prescribing information, including boxed warning.

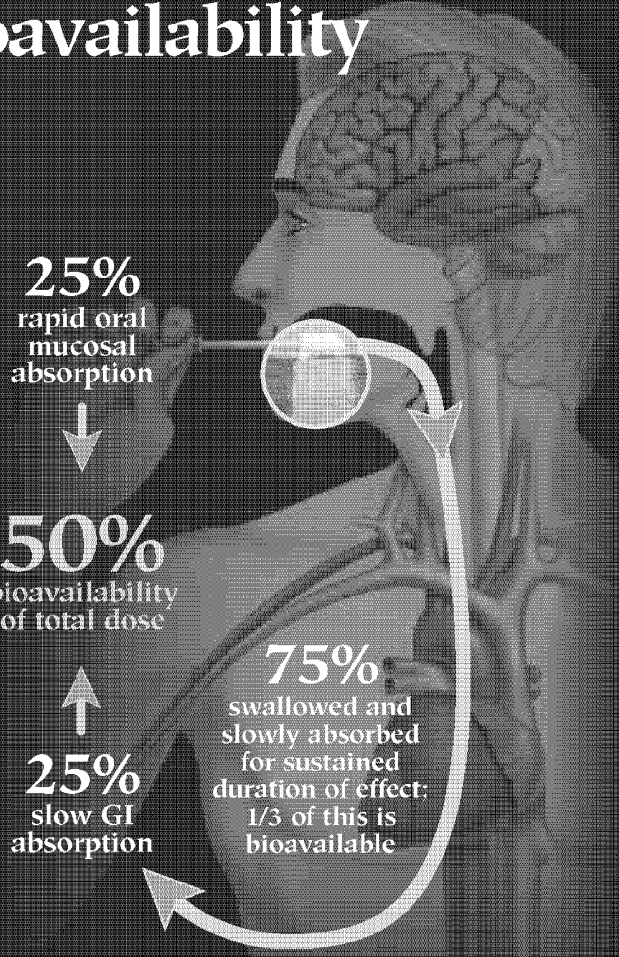
Bioavailability

The ACTIQ® matrix dissolves rapidly[1]

- 62% dissolves in 5 minutes*
- 93% dissolves in 10 minutes*

*Based on *in vitro* studies.

- Longer or shorter consumption times than the recommended 15 minutes may produce less efficacy than reported in clinical trials[2]



- The ACTIQ unit should not be chewed or swallowed as that might result in lower peak concentrations and bioavailability than when consumed as directed[2]
- Both the blood fentanyl profile and bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction that is swallowed[2]

Efficacy

Actiq® (oral transmucosal fentanyl citrate)

With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[2]

- Median time to maximum plasma concentration (T_{max}) across 4 doses of ACTIQ varied from 20-40 minutes as measured after the start of administration
- ACTIQ produced significantly ($P<0.0001$) more pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration in opioid tolerant cancer patients

Duration of pain relief[2]

- In clinical trials, pain relief was observed at 1 hour (the last time measured) following administration of the ACTIQ unit
- 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)

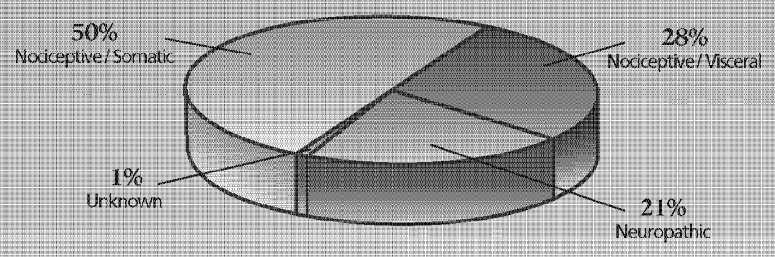
Efficacy established with long-acting pain therapy

- Efficacy demonstrated in opioid tolerant cancer patients receiving both long-acting oral and transdermal opioids[2,5]
- 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**[2]
- The most serious adverse events 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[2]
- The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, and dizziness[2]

Please see accompanying full prescribing information, including boxed warning.

Types of BTCP in clinical trials of ACTIQ®

Cancer pain pathophysiology (N=219)[5-7]



- In a randomized, double-blind, placebo-controlled trial, efficacy was evaluated in opioid tolerant cancer patients receiving both long-acting oral and transdermal opioids (N=92)[5-7]
  - 63 patients on oral morphine; 21 patients on transdermal fentanyl; 8 patients on other opioids
  - Pain types: nociceptive/somatic 53%; nociceptive/visceral 31%; neuropathic 15%; unknown 1%
  - ACTIQ produced significantly more pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration in opioid tolerant cancer patients

With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[2]

ACTIQ clinical trials: dosing

Actiq® (oral transmucosal fentanyl citrate) [C-II]

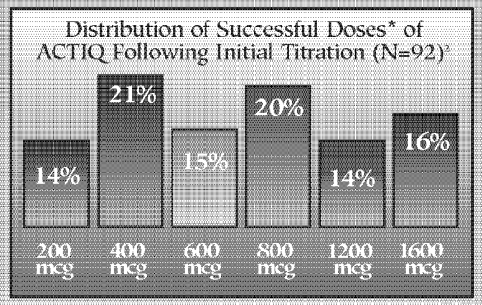
Dose titration studies

- 75% of patients found a successful dose* of ACTIQ[2]
- Regardless of pain pathophysiology, patients titrated to the same mean dose of 600 mcg[6,7]
- No difference in efficacy was noted in patients randomized to start on either 200 mcg or 400 mcg.[6,7] The package insert recommends a starting dose of 200 mcg[1]

Randomized, double-blind, placebo-controlled trial[5]

- Patients started on 200 mcg titrated to a mean maintenance dose of 789 mcg[†]
- 86% of patients were titrated to 400 mcg or higher
- 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

Distribution of Successful Doses* of ACTIQ Following Initial Titration (N=92)[5]



*Successful dose=1 dosage strength of ACTIQ could be used consistently for at least 2 consecutive days to treat BTCP without unacceptable side effects.

†Dosage required to manage BTCP could not be predicted by dosage of long-acting medication.[5,6]

Please see accompanying full prescribing information, including boxed warning.

Important Warnings

- 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**
- 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 nontolerant patients
- Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer
- Instruct patients/caregivers that ACTIQ can be fatal to a child. Keep all units from children and discard properly
- The most common side effects observed were somnolence, nausea, vomiting, and dizziness
- 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

Dosing and titrating to optimize therapy

Actiq® (oral transmucosal fentanyl citrate) CII

1

Titration R_x

ACTIQ 200 mcg

Disp six units
Sig: Dissolve one unit in mouth over 15 min.

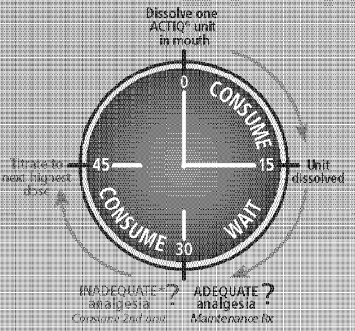
Repeat PRN 1x. 15 min after consumption of first unit
No more than 2 units/episode

MD

For illustration purposes only.

- Titrate to a dose that provides adequate analgesia and minimizes side effects
- In titration process, no more than 2 units should be taken for each pain episode
- 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
- **Longer or shorter consumption times then the recommended 15 minutes may produce less efficacy than reported in clinical trials[2]**

2



- The initial dose of ACTIQ to treat episodes of breakthrough cancer pain should be 200 mcg
- 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 2 units should be taken for each individual breakthrough cancer pain episode

*If treatment of several consecutive breakthrough cancer pain episodes requires more than one ACTIQ unit per episode, return to top of diagram using next highest dosage strength.

3

Maintenance R_x

ACTIQ 800 mcg

Disp one hundred twenty units

Sig: 1 unit PRN up to 4x/day

MD

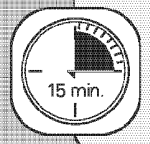
For illustration purposes only.

- Once a successful maintenance dose has been found, patients should limit their consumption to 4 or fewer units per day
- ACTIQ is packaged as individual units and boxed in multiples of 30

CUT open the child-resistant blister pack when you are ready to use ACTIQ. Remove the ACTIQ unit.

CONSUME the ACTIQ unit by dissolving it in your mouth between your cheeks and gums. Move ACTIQ around in your mouth, especially along your cheeks. Twirl the handle often. Do not bite or chew ACTIQ.

• Use only one ACTIQ unit per episode • If your doctor says you can take more than one ACTIQ per episode, no more than 2 units should be taken for each episode of pain • ONLY use the second unit 15 minutes after you have finished the first unit (or 30 minutes after you started the first unit) • Once you are able to treat an average episode with a single unit, you should not take more than 4 units per day • 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 should not eat or drink anything while taking ACTIQ

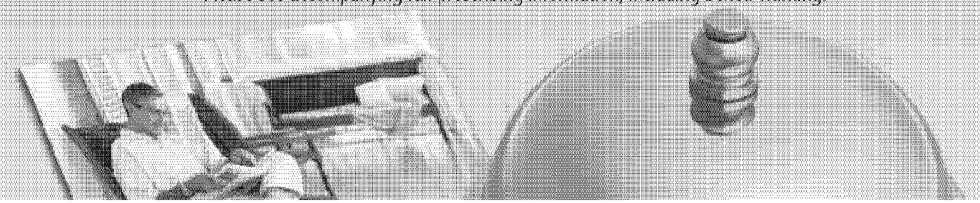


CLOCK for 15 minutes – the recommended dosing time. You need to finish the ACTIQ unit completely in 15 minutes to get the most relief. If you finish ACTIQ too quickly, you will swallow more of the medicine and get less relief.

- With ACTIQ, pain relief may be observed in 15 minutes, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit[2]
- 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**[2]
- The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, and dizziness[2]
- The most serious adverse events 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[2]

Please see accompanying full prescribing information, including boxed warning.

- 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[2]
- **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 and to discard opened units properly**[2]
- 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 pack, yet may contain enough medicine to be fatal to a child[2]



Side effect profile

- The most common side effects observed in ACTIQ® clinical trials were somnolence, nausea, vomiting, and dizziness[1]
- Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose[1]
- The most serious adverse events 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[1]
- ACTIQ should be titrated with caution in patients with chronic obstructive pulmonary disease or other medical conditions predisposing them to hypoventilation. Hypoventilation may occur more readily when opioids are given in conjunction with other agents that depress respiration[1]

Prescribing safety

- 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[1]
- This product must not be used in opioid nontolerant patients. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer[1]
- 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 and to discard opened units properly[1]
- 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 pack, yet may contain enough medicine to be fatal to a child[1]

Important Warnings

– ACTIQ is a CII medication

– ACTIQ is to be used only by the patient for whom it is dispensed

– ACTIQ may be habit forming

Other important safety information

Actiq® (oral transmucosal fentanyl citrate) CII

ACTIQ Risk Management Program (RMP)

- ACTIQ was the first opioid approved with a comprehensive RMP
- The ACTIQ RMP has been designed to address 3 key potential risk situations: accidental ingestion by children, improper patient selection, and diversion or abuse

Patient Safety Features

- Child-resistant unit-dose packaging
- Dosage strength marked on both lozenge and handle
- Safety icons used throughout

Patient Welcome Kit

- Child-resistant safety lock
- Secure personal holder
- Child-resistant storage container
- Patient leaflet
- Warning stickers & magnet for the home
- Children's booklet
- Patient diary
- Notification flyer

Professional Materials

- Patient education video
- www.actiq.com

Professional Services

- Medical information
- Welcome kit hotline
- Patient education materials

1-800-896-5855

- 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**[1]

Please see accompanying full prescribing information, including boxed warning.

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Breakthrough pain: definition, prevalence and characteristics

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Summary In the cancer population, the term breakthrough pain typically refers to a transitory flare of pain in the setting of chronic pain managed with opioid drugs. The prevalence and characteristics of this phenomenon have not been defined, and its impact on patient care is unknown. We developed operational definitions for breakthrough pain and its major characteristics, and applied these in a prospective survey of patients with cancer pain. Data were collected during a 3 month period from consecutive patients who reported moderate pain or less for more than 12 h daily and stable opioid dosing for a minimum of 2 consecutive days. Of 63 patients surveyed, 41 (64%) reported breakthrough pain, transient flares of severe or excruciating pain. Fifty-one different pains were described (median 4 pains/day; range 1–3600). Pain characteristics were extremely varied. Twenty-two (43%) pains were paroxysmal in onset; the remainder were more gradual. The duration varied from seconds to hours (median/range: 30 min/1–240 min), and 21 (41%) were both paroxysmal and brief (lancinating pain). Fifteen (29%) of the pains were related to the fixed opioid dose, occurring solely at the end of the dosing interval. Twenty-eight (55%) of the pains were precipitated; of these, 22 were caused by an action of the patient (incident pain), and 6 were associated with a non-volitional precipitant, such as flatulence. The pathophysiology of the pain was believed to be somatic in 17 (33%), visceral in 10 (20%), neuropathic in 14 (27%), and mixed in 10 (20%). Pain was related to the tumor in 42 (82%), the effects of therapy in 7 (14%), and neither in 2 (4%). Diverse interventions were employed to manage these pains, with variable efficacy. These data clarify the spectrum of breakthrough pains and indicate their importance in cancer pain management.

Key words: Cancer pain; Breakthrough pain; Opioids; Pain management

Introduction

The term, breakthrough pain, has become accepted in the lexicon of the cancer pain specialist and refers generally to a transitory exacerbation of pain that occurs on a background of otherwise stable pain in a patient receiving chronic opioid therapy. In the population of cancer pain patients, breakthrough pain is frequently mentioned as a clinical problem, and supplemental opioid doses are often suggested to manage it when it occurs [6,10,17]. Access to these supplemental, or 'rescue,' doses of an opioid during chronic opioid therapy is now commonly recommended [10], and this can be taken as further evidence of the clinical recognition that transient pains often complicate the efficacy of analgesic therapy in cancer patients.

Given this recognition, it is remarkable to note that the phenomenon of breakthrough pain has never been assessed empirically. Although it is evident that transient pains have protean characteristics, their prevalence and specific features have not been evaluated. The relationship of these

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0304-3959/90/$03.50

pains to factors associated with the patient, the neoplasm or anti-neoplastic therapies is unknown, and the efficacy of therapeutic interventions has never been determined. In short, despite clinical experience indicating that transient pains are a common and often difficult problem, an acceptable definition for breakthrough pain is lacking and the phenomenology described by this term is obscure.

Methods

To determine the prevalence and characteristics of breakthrough pain, a brief questionnaire was developed and used in a prospective survey of cancer pain patients. Pilot data from this survey have been reported previously [12].

Survey instrument

Given the paucity of information about transitory pains in cancer patients, and the likelihood that the clinical use of the term 'breakthrough pain' encompasses a diverse group of painful experiences, a broad definition was applied in this survey. Although it was recognized that most patients would be receiving opioids, it was decided a priori that opioid use was not a reasonable criterion for the definition of these pains. Rather, worsening of pain intensity and a temporal profile characterized by transience were the key criteria in this operational definition, as follows:

Breakthrough pain was defined as a transitory increase in pain to greater than moderate intensity (that is, to an intensity of 'severe' or 'excruciating'), which occurred on a baseline pain of moderate intensity or less (that is, no pain or pain of 'mild' or 'moderate' intensity). *Baseline pain* was defined as that reported by the patient as the average pain intensity experienced for 12 or more hours during the 24 h prior to the interview. Patients whose baseline pain was severe or worse were said to have uncontrolled pain and were not assessed for breakthrough pain.

The specific features of breakthrough pain evaluated in the questionnaire were derived from principles of cancer pain assessment [10,16–18] and clinical experience (Table I). For the purposes of the survey, these characteristics were defined as follows:

Temporal characteristics. Breakthrough pains were characterized by frequency, type of onset, and duration. The onset of a breakthrough pain was defined as the time required for the pain to progress from first perception to maximal intensity; to improve reliability, this variable was dichotomized as paroxysmal (maximal in intensity within 3 min) versus gradual (longer than 3 min). Duration, as recalled by the patient, was recorded in minutes.

Pain severity. Pain severity was assessed using a 5-point categorical scale ('none,' 'slight,' 'moderate,' 'severe,' and 'excruciating'). By definition, all breakthrough pains had been rated by the patient as either severe or excruciating.

Pain location. The location of the breakthrough pain was noted and compared to the location of the baseline pain.

TABLE I

CHARACTERISTICS OF BREAKTHROUGH PAINS

Pain severity
Pain location
Temporal characteristics
Frequency
Onset
Duration
Relationship to fixed analgesic dose
Precipitating event
None (spontaneous)
Incident
Non-volitional precipitants
Predictability *
Pathophysiology
Somatic
Visceral
Neuropathic
Mixed
Etiology
Related to neoplasm
Related to treatment
Unrelated to neoplasm or treatment
Palliative factors

* Not assessed in this survey.

Relationship to the regularly scheduled analgesic. Although opioid use was not included in the definition of breakthrough pain, most patients were receiving regular doses of these drugs. Patients were assessed for a relationship between the analgesic regimen and transitory pains by noting whether pains occurred or markedly worsened at the end of a dosing interval.

Precipitating events. Each breakthrough pain was characterized as spontaneous, occurring without an identifiable precipitating event, or precipitated. Precipitated pains induced by an action of the patient, such as movement, swallowing, micturition, defecation or cough (commonly known as 'incident pains') were distinguished from those in which the precipitant was non-volitional.

Pathophysiology. The underlying mechanism for the breakthrough was characterized as somatic, visceral or neuropathic [2,5,6,10,15,18], as follows: Somatic pains were related to an etiology that involved somatic structures, such as bone or muscle, and were described, at least in part, as aching, stabbing or throbbing. Visceral pains were related to a lesion in a hollow or solid viscus and were described, at least in part, as diffuse, gnawing or crampy if hollow viscus was involved, or aching or sharp if a solid viscus was involved. Neuropathic pains were related to a lesion involving peripheral or central afferent neural pathways and were described, at least in part, as unfamiliar, burning or lancinating. The pathophysiology was labeled mixed if these criteria were not met or multiple concurrent processes were observed.

Etiology. Etiologies were grouped into those related to the neoplastic lesion, to an anti-neoplastic therapy, or to neither the cancer nor its treatment.

Palliative factors. Patients were asked to describe the specific factors they believed to be responsible for the cessation of the transient flare of pain.

Survey methodology

All adult inpatients consecutively referred for evaluation and treatment by the Pain Service at Memorial Sloan-Kettering Cancer Center during a 3 month period were considered to be candidates for the survey. All patients were evaluated by one of the authors (NH). Consistent with the standard approach to these patients, the clinical evaluation was usually followed by administration of an analgesic drug or adjustment of the current dose of the analgesic in use. Daily evaluation resulted in dosage increments in most patients following the initial consultation.

Patients who achieved relatively stable doses (defined as less than 20% increase in opioid dose per day) for 2 consecutive days were queried about breakthrough pain. Patients were first asked whether or not they would endorse the statement that, on average, pain was absent, mild or moderate for more than 12 h during the prior 24 h. Patients who answered negatively to this question were considered to have uncontrolled pain and were not evaluated further. Patients who agreed, however, were then asked whether or not they had experienced temporary flares of severe or excruciating pain during this period. Patients who responded affirmatively to the latter question were considered to have breakthrough pain and were administered the remainder of the pain-related questions. In addition, demographic data, analgesic history and information about disease status and anti-neoplastic therapies were also collected from all patients.

Group comparisons were performed using chi-square or *t* tests.

Results

Ninety patients were evaluated during this 3 month period. Seventy achieved the initial criterion of stable opioid dosing for 2 or more days. Sixty-three (90%) of these patients reported pain of moderate intensity or less for greater than 12 h/day during the day prior to the interview. Of these patients with stable opioid dose and moderate pain or less, 41 (63%) described one or more breakthrough pains during the preceding 24 h. Specifically, 32 noted 1 type of breakthrough pain, 8 identified 2 distinct types, and 1 reported 3 types. Thus, these 41 patients represented 51 breakthrough pain syndromes.

Demographics, analgesic consumption and tumor-related information about these patients is

TABLE II

NUMBER (%) OF PATIENTS WITH BREAKTHROUGH PAINS AND SPECIFIC DEMOGRAPHIC, ANALGESIC AND ONCOLOGIC CHARACTERISTICS

N = 41 patients

Age: Median: 51 years Range: 15–81 years	
Sex: Male 19 Female 22	
Tumor diagnosis	
Genitourinary	11
Head/neck	5
Gastrointestinal	4
Lung	3
Sarcoma	3
Unknown primary	3
Breast	2
Melanoma	2
Other	8
Extent of disease	
Remission	3
Local extension	1
Metastatic	37
Opioid consumption during the previous 24 h (in intramuscular morphine equivalent milligrams *)	
1–20	9
21–40	9
41–60	5
61–80	2
81–100	2
>100	10
No opioids	4

* Based on standard relative potency tables, using an oral : intramuscular conversion for morphine of 3 : 1.

described in Table II. There were no significant differences between those patients fulfilling the criteria for breakthrough pain and those without this phenomenon on any of these characteristics.

The number of breakthrough pain episodes during the 24 h period varied widely among patients. The median number of breakthrough pains was 4 (range 1–3600 pains). Fifteen patients described 1–3 painful episodes, 14 noted 4–6 pains, 7 reported 7–10 pains, and 5 patients had more than 10 breakthrough pains during the prior day. The maximum number was reported by a patient with lung cancer who experienced a brief and stabbing somatic pain in the region of a rib fracture that occurred with a paroxysm of cough every minute.

An onset within 3 min was described in 22 (43%) of the 51 pains; the remainder required longer to reach maximal intensity. The median duration of the pains was 30 min (range 1–240 min), including 21 pains reported to persist for 20 min or less. Twenty-one (41%) pains were characterized by both rapid onset and brief duration.

As noted, severity was one of the criteria used to define breakthrough pain. All breakthrough pains, therefore, were severe or excruciating in intensity, and these data cannot be used to clarify the range of pain intensity that characterizes transient pains in cancer patients.

All patients with breakthrough pain also experienced at least one continuous pain, which in most cases was managed in part with a fixed dose opioid regimen. The location of these persistent pains varied widely among patients. Breakthrough pains usually, but not always, occurred in the same location. Specifically, 49 (96%) of the breakthrough pains were propinquitous to a more continuous pain, whereas 2 (4%) were reported to be an entirely new site of pain. Most cases of breakthrough pain therefore represented a transient exacerbation of a pain already experienced.

Pain onset or a marked worsening of the pain occurred at the end of the dosing interval of the regularly scheduled analgesic in 15 (29%) pains (14 patients). The scheduled analgesic in all but 4 patients was an opioid. These breakthrough pains were not significantly different from pains unrelated to the analgesic regimen in frequency, type of onset, duration, prevalence of specific precipitants, pathophysiology or etiology.

Each breakthrough pain was characterized, if possible, by the precipitant that preceded it (Table III). Precipitants were identified prior to 28 (55%) pains. Most of these precipitating events were volitional, and the resultant breakthrough pain can thus be termed an 'incident' pain. Some of the pains that were related to the analgesic regimen were also characterized by other specific precipitants. Six (12%) pains could be attributed to both end of dose failure and a specific precipitant; 9 (18%) were characterized by a relationship to the dose alone, and 22 (43%) had a precipitant unre-

TABLE III

PRECIPITATING EVENTS FOR BREAKTHROUGH PAIN

N = 51 pains.

No identified precipitant	23
Precipitants	28
Volitional (incident)	
Movement in bed	7
Walking	4
Cough	6
Sitting	2
Standing	2
Touch	1
Non-volitional	
Bowel distension	4
Ureter/renal pelvis distension	1
Medication regurgitated *	1

* Pain flare following regurgitation of a single dose of opioid drug.

lated to the analgesic dose. The remainder of the pains (14 pains or 27% of the total sample) were completely idiopathic.

Seventeen (33%) pains were somatic, 10 (20%) were visceral, 14 (27%) were neuropathic, and 10 (20%) were mixed. There were no significant differences in any of the demographic or pain-related variables among the pathophysiologies, but the sample size in this survey was insufficient to validly assess these relationships. Of note, there was no relationship between the pathophysiology and rapid onset of the pain, as defined previously. Of 22 pains with rapid onset, 9 (41%) were somatic, 3 (14%) visceral, 6 (27%) neuropathic and 4 (18%) mixed.

Thirty-nine (76%) breakthrough pain syndromes were specifically related to a known neoplastic lesion. Ten (20%) could be attributed to an effect of an anti-neoplastic therapy, and 2 (4%) were unrelated to either the cancer or its treatment. Again, the sample size was too small to allow valid group comparisons, and relationships between the etiology of breakthrough pain and other variables remain conjectural.

Most patients could identify specific interventions that either aborted the pain or reduced the frequency or intensity of subsequent pains (Table IV). Importantly, many of these palliative factors were not provided by the medical staff, but were rather discovered by the patient through trial and error to be useful in mitigating or forestalling the pain.

TABLE IV

PALLIATIVE FACTORS REPORTED BY PATIENTS TO BE USEFUL IN ALLEVIATING A BREAKTHROUGH PAIN OR REDUCING ITS FREQUENCY OR INTENSITY

Some patients had more than one palliative factor.

Use of rescue dose	16
Change in position or movement	13
Use of rescue dose and change in position	2
Use of regularly scheduled dose	6
Miscellaneous	9
Defecation	2
Flatus	1
Suppressed cough	3
Antacid	1
Sleep	1
Squeeze painful region	1
No intervention known to the patient	5

Discussion

This survey is the first devoted to the cancer pain phenomenon generally known as breakthrough pain. It was undertaken to highlight this clinical problem in cancer pain management, define it explicitly as a point of departure for future investigations, and begin to clarify its prevalence and characteristics.

Several important criticisms of the present survey are possible. These may limit the generalizability of some of the data and must be addressed in future studies of breakthrough pain. First, the study population was referred to a Pain Service at a large cancer hospital and was therefore unquestionably selected for difficult pain problems. The prevalence of transient pains determined in this survey may therefore be higher than other groups of cancer pain patients. Second, the operational definitions employed in this survey, while clearly more precise than current descriptions in the clinical literature [1–4,9,10], may also introduce bias. For example, the decision to exclude opioid use from the definition of breakthrough pain could

potentially exaggerate the prevalence by labeling as breakthrough pain some painful experiences that most practitioners would exclude. Third, there has been no independent validation of the survey instrument. Indeed, several of the factors assessed, such as pain pathophysiology, are themselves constructs in need of validation. Finally, there was a potential for observer bias in using one of the treating clinicians as the interviewer, as well as bias in relying on patient recall for events during the preceding 24 h. Additional studies of breakthrough pain are needed to replicate the findings of this survey in different populations and address these potential methodological problems.

Prevalence and characteristics of breakthrough pains

Transient pains were extremely prevalent in this population of cancer patients referred for pain management. Not surprisingly, the characteristics of these pains were highly diverse. The proximate cause could be related to an insufficient amount of analgesic drug, a specific precipitant, or both; less than one-third were fully idiopathic. Other features, including the temporal profile, location, pathophysiology and type of underlying etiology, were similarly variable.

This variability in breakthrough pain syndromes was such that no substantial group differences could be discerned. Although surveys with larger samples may yet discover relationships between specific characteristics of breakthrough pain and demographic or clinical features of the patient, the data available suggest that, unlike syndromes associated with more persistent cancer pain [11], breakthrough pains cannot be characterized in a manner that yields broad implications for lesion recognition, pain pathogenesis or prognosis.

Among the most important characteristics of these transient pains is the relationship to the baseline analgesic regimen. The present survey inferred a relationship between the analgesic dose and breakthrough pain from the phenomenon of end-of-dose onset or exacerbation of pain. Although this is reasonable, it must be noted that better evidence would be provided by the observation that these pains improve with an increase in dose or a shortening of the dosing interval, maneuvers that this survey was not designed to assess. Nonetheless, it can be postulated that some breakthrough pains are related to baseline opioid dose, and that this may be true even when a change at the end of the dosing interval cannot be demonstrated (e.g., with continuous infusion techniques). This does not negate the common observation that incident pains, which are herein considered to be a subtype of breakthrough pain, tend to respond less well to opioids than continuous pains [13], but does contradict the conclusion that these pains are intrinsically resistant to opioid treatment.

Breakthrough pains with rapid onset also comprise an important subgroup. The present survey defined this characteristic as maximal pain intensity within 3 min. This criterion was employed despite the possibility that it could obscure the prevalence of specific pain patterns that may have unique clinical features. The broader definition, however, recognized the difficulties expressed by patients in recalling this characteristic reliably and was more likely to capture the spectrum of rapid onset breakthrough pains. It was anticipated that neuropathic mechanisms would be overrepresented among pains of rapid onset and brief duration. Such neuropathic pains are important to identify since there is clinical evidence that they may be particularly responsive to specific drugs, such as some anticonvulsants [14]. Surprisingly, this survey demonstrated that somatic and visceral pathophysiologies were as common in pains of this type as neuropathic mechanisms. Although it remains possible that some types of brief pains, such as those with maximal intensity at onset, may indeed be typical of a neuropathic mechanism, these results indicate that brief pains with rapid onset may have variable mechanisms and suggest the need for careful assessment in the clinical setting.

The great variety of precipitating events was another important finding of this survey. Contrary to assumptions that appear in the clinical literature, some precipitating events clearly identified by the patient were not under voluntary control and did not, therefore, conform to the usual definition of incident pain. Recognition of these nonvolitional precipitants is important, since they,

like those under voluntary control, may be amenable to treatment.

The identification of precipitants relates closely to a facet of breakthrough pain, predictability, that was not assessed in the present survey. Predictability of pain appeared to be a salient characteristic in these patients, influencing the distress caused by the pain and the options available for therapy. It is likely that there is an association between the predictability of the pain and both the type and reliability of the precipitant. This feature should be assessed in future surveys of breakthrough pain.

These data also suggest that breakthrough pains can be usefully distinguished by presumed pathophysiology and etiology. These constructs are commonly employed by clinicians to select adjunctive therapies (e.g., non-steroidal anti-inflammatory drugs for bone pain) and determine prognosis. Similarly, they appear to be useful in selecting a treatment approach for the breakthrough pain.

Patients reported benefit from a great variety of interventions for breakthrough pain. Some were offered by the medical staff, but many, such as changes in position, were discovered fortuitously by the patient. Given the likelihood that many of the pains remit spontaneously after a short time, it is probable that some patients attributed benefit to interventions that actually had little impact. Future investigations will also need to clarify these therapeutic considerations more systematically.

An approach to the management of breakthrough pain

Many published guidelines for the therapy of cancer pain [1,6,7,10,16,17] allude to the problem of transient exacerbation of pain, but none describes the management of this problem beyond the use of supplemental doses of an opioid. The experience detailed in this survey indicates that a more comprehensive approach is needed.

Four principles can be proposed to guide the management of breakthrough pain. First, the variability observed in this survey indicates the importance of a comprehensive assessment in the clinical approach to these pains. This evaluation should determine pain characteristics, etiology and pathophysiology, and the relationship of the pain to the patient's overall clinical status.

Second, consideration should be given to primary treatment of the underlying etiology. Primary treatments include a variety of approaches, such as radiotherapy to a painful lesion, surgical repair of a fractured bone, decompression of obstructed bowel, and administration of antibiotics for a localized infection. The feasibility, risks and potential benefits of these treatments vary from patient to patient, and the successful implementation of any requires careful assessment and appropriate patient selection.

Third, given the relationship between the occurrence of breakthrough pains and baseline analgesic (usually opioid) regimen, adjustments in the dose of the regularly scheduled analgesic should be considered in every case. Specifically, the dose of this opioid should be increased until either favorable effects occur or intolerable and unmanageable side effects supervene. In this situation, limiting side effects typically occur during the intervals between the severe pains [7].

Finally, primary analgesic approaches directed specifically at the breakthrough pain must be considered. Clinical experience indicates that the most important approach entails the use of an opioid 'rescue dose,' a supplemental 'as needed' dose offered concurrently with the regularly scheduled drug. Although neither the pharmacokinetics nor the pharmacodynamics of the 'rescue dose' has been studied, an opioid with a short half-life and rapid onset of action can be recommended empirically; if the regularly scheduled opioid has a short half-life, this drug can also be selected as the 'rescue.' Although management is simplified if the same route of administration is used for both the 'rescue' and the fixed dose, occasional patients on oral dosing find that the onset of action of an oral dose is too slow and have better results with a parenteral 'rescue.' The recent advent of patient-controlled analgesia systems in devices capable of delivering continuous infusion, particularly ambulatory infusion pumps for continuous subcutaneous infusion, can, if available, expedite the administration of supplemental doses in those receiving opioid infusions.

The dose of an opioid 'rescue' must reflect the

level of the baseline dose. Some clinicians begin with a dose roughly equivalent to 5–10% of the total daily opioid intake administered every 2–3 h as needed. However, the size of the most effective dose that does not produce intolerable side effects is unknown in any individual case, and titration of the 'rescue dose' should be viewed as a key principle in the management of breakthrough pain by this approach.

Other pharmacological approaches may be useful in some types of breakthrough pain. As noted, there is substantial evidence that patients with lancinating neuropathic breakthrough pains may respond to an adjuvant analgesic, such as an antidepressant or anticonvulsant [10,14]. Some patients with breakthrough pain related to neoplastic invasion of bone or nerve trunk appear to benefit, at least temporarily, from the administration of a corticosteroid. The use of specific drugs to reduce the frequency of precipitating events, such as antitussives, laxatives, antiperistaltic drugs or agents that may reduce muscle spasm, may also be effective.

Non-pharmacologic approaches should also be considered. Physiatric techniques, such as physical therapy or the use of orthotics, may ameliorate the musculoskeletal complications that predispose to breakthrough pains; bracing of the painful part may be very useful in patients with severe movement-related pain. Some patients appear to benefit from psychological techniques [4], such as distraction. Anesthetic approaches that are commonly used in the treatment of chronic cancer pain are sometimes beneficial in those with breakthrough pain; in particular, some patients clearly benefit from chemical neurolysis, the purpose of which is to deafferent the painful part [8]. Continuous epidural local anesthetic infusion is a new anesthetic technique that obviates some of the risks involved in neurolysis and may prove to be very useful in the treatment of breakthrough pain [1,9]. Finally, surgical deafferentation of the painful part, by cordotomy for example, can also be considered in selected patients with refractory breakthrough pain. There is evidence that patients with a peripheral nociceptive lesion are more likely to respond to such procedures than those with a painful neuropathic lesion associated with deafferentation [15].

This survey demonstrates that transient pains in cancer patients are common and diverse in presentation. The clinical literature on cancer pain does little to illuminate the manifestations or impact of these pains and, indeed, may have obscured the variability of these phenomena. Additional surveys are needed to categorize these pains and relate their clinical presentation to underlying etiology and pathogenesis. Studies of treatments for breakthrough pains, such as the 'rescue dose,' are clearly needed.

Acknowledgement

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ACTIQ®

(oral transmucosal fentanyl citrate)

CII

1598.02

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

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

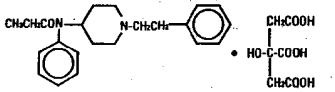
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

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

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

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

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

Clinical Pharmacology

Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

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

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

Respiratory System:

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC®) administration and may persist for several hours.

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

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

Pharmacokinetics

Absorption:

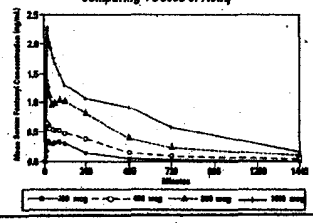
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary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

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

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

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0-\infty}$ 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	800 mcg	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 (28)	0.76 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (% CV)	102 (66)	243 (67)	573 (64)	1026 (67)
$t_{1/2}$, minute mean (% CV)	193 (48)	386 (115)	361 (55)	358 (45)

Distribution:

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (Vss) was 4 L/kg.

Metabolism:

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

Elimination:

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

Special Populations:

Elderly Patients:

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

Patients with Renal or Hepatic Impairment:

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

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

Gender

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

CLINICAL TRIALS

Breakthrough Cancer Pain:

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered

(200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

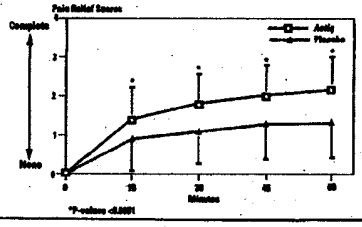
Table 2
Successful Dose of Actiq Following Initial Titration

Actiq Dose	Total No (%) (N=92)
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean ±SD	789±468 mcg

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

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

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



*P-values <0.0001

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

INDICATIONS AND USAGE

(See BOX WARNING and CONTRAINDICATIONS)

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Actiq should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see **DOSAGE AND ADMINISTRATION**).

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

CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. The risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see **Pharmacokinetics**). This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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

WARNINGS

See BOX WARNING

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

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

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

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for specific patient instructions.)

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

PRECAUTIONS

General

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

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking *Actiq* should be warned of these dangers and should be counseled accordingly.

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

Hypoventilation (Respiratory Depression)

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Cardiac Disease

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

Hepatic or Renal Disease

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

Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS,** and **PATIENT LEAFLET** for specific patient instructions.)

Frequent consumption of sugar-containing products may increase the risk of dental decay (each *Actiq* unit contains approximately 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking *Actiq* (see **ADVERSE REACTIONS** - Post-Marketing Experience). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using *Actiq* should consult their dentist to ensure appropriate oral hygiene.

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

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

Disposal of Used *Actiq* Units

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

1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Disposal of Unopened *Actiq* Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

1) Remove the *Actiq* unit from its blister package using scissors, and hold the *Actiq* by its handle over the toilet bowl.
2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3) Dispose of the handle in a place that is out of the reach of children.
4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, blister packages, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

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

Laboratory Tests

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

Drug Interactions

See **WARNINGS**.

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

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

Pregnancy - Category C

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Actiq is not indicated for use in labor and delivery.

Nursing Mothers

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

Pediatric Use

See WARNINGS.

Geriatric Use

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

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

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

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

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

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

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

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

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of *Actiq* that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Table 3.

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

Dose Group	200-600 mcg	601-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	230	130	94	41	254
Body As A Whole					
Asthenia	6	4	6	7	9
Headache	5	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	19	11	32	20
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	8	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	5	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

The following adverse events not reflected in Table 3 occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anoraxia, 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	200-600 mcg	601-1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	88	93	83	27	152
Body As A Whole					
Asthenia	25	30	17	15	28
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	8
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	39	25	26	46
Vomiting	24	26	19	7	32
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	19	6	0	16
Anxiety	9	6	6	7	15
Somnolence	6	13	5	7	15
Confusion	3	5	13	7	10
Depression	9	6	2	7	9
Insomnia	5	1	6	4	7
Abnormal Gait	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	6	4	5
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	11	16	8	7	22
Skin					
Rash	3	5	0	4	5
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

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

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness
Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of *Actiq*. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to *Actiq*.

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

DRUG ABUSE AND DEPENDENCE

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

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

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

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

The handling of *Actiq* should be managed to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law (see **SAFETY AND HANDLING**).

OVERDOSAGE

Clinical Presentation

The manifestations of *Actiq* overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation (see **CLINICAL PHARMACOLOGY**).

General

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

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

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

Treatment of Overdose in Opioid-Tolerant Patients

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

General Considerations for Overdose

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

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

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

DOSAGE AND ADMINISTRATION

***Actiq* is contraindicated in non-opioid tolerant individuals.**

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

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

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

Administration of *Actiq*

The blister package should be opened with scissors immediately prior to product use. The patient should place the *Actiq* unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The *Actiq* unit should be sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

The *Actiq* unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in *Actiq* clinical trials. If signs of excessive opioid effects appear before the unit is consumed, the drug matrix should be removed from the patient's mouth immediately and future doses should be decreased.

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

Dose Titration

Starting Dose: *The initial dose of Actiq to treat episodes of breakthrough cancer pain should be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

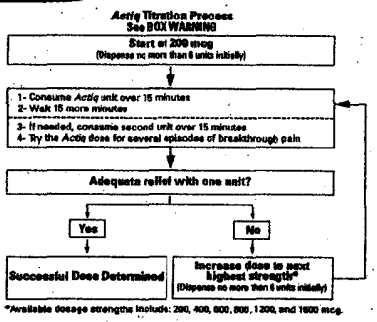
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



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

Dosage Adjustment

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

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

Discontinuation of *Actiq*

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

SAFETY AND HANDLING

Actiq is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see **BOX WARNING, WARNINGS, PRECAUTIONS** and **PATIENT LEAFLET**).

Store at 20-25°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.)

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

DISPOSAL OF ACTIQ

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

A temporary storage bottle is provided as part of the *Actiq* Welcome Kit (see **Information for Patients and Their Caregivers**). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required, referral to the *Actiq* 800# (1-800-896-5855) should be made.

HOW SUPPLIED

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

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

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the solid drug matrix, the handle tag, the blister package and the carton. See blister package and carton for product information.

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

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

℞ only.

DEA order form required. A Schedule CII narcotic.

Manufactured by:
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Absorption and Bioavailability of Oral Transmucosal Fentanyl Citrate

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Oral transmucosal fentanyl citrate (OTFC) is a novel, noninvasive dosage form of fentanyl used to provide children and adults with sedation, anxiolysis, and analgesia. In order to determine the bioavailability and absorption of fentanyl from OTFC, 12 volunteers were given intravenous fentanyl citrate or OTFC 15 μg/kg on each of two occasions. On a third occasion, the authors assessed oral administration (gastrointestinal absorption) by giving eight of the same volunteers the same dose of a solution of fentanyl citrate to swallow. In each study, arterial blood samples were taken over 24 h for analysis of plasma fentanyl. After intravenous (iv) administration of fentanyl, clearance (mean ± standard deviation) was 0.67 ± 0.15 l/min; volume of distribution at steady state was 287 ± 79 l; and the terminal elimination half-life was 425 ± 102 min. Peak plasma concentrations of fentanyl were higher (3.0 ± 1.0 *vs.* 1.6 ± 0.6 ng/ml, $P = 0.01$) and occurred sooner (22 ± 2.5 *vs.* 101 ± 48.8 min, $P = 0.003$) after OTFC than after oral solution administration. Plasma concentrations of fentanyl after OTFC decreased rapidly, to less than 1.0 ng/ml within 75–135 min after the beginning of administration. Peak absorption rate was greater (11.1 ± 4.3 *vs.* 3.6 ± 2.1 μg/min, $P = 0.004$) and occurred much sooner after OTFC than after oral solution administration (19 ± 2.6 *vs.* 87.5 ± 38.1 min, $P = 0.001$). Systemic bioavailability was greater after OTFC administration than after the oral solution (0.52 ± 0.1 *vs.* 0.32 ± 0.1, $P = 0.01$). Terminal elimination half-life was similar after all modes of fentanyl delivery—OTFC (460 ± 313 min), iv (425 ± 102 min), or oral solution (469 ± 123 min). These results suggest that although absorption of fentanyl from OTFC occurs through both the oral mucosa and the gastrointestinal tract, it is more rapid at the former. The data also indicate that sequestration of fentanyl in the oral mucosa is minimal. (Key words: Analgesia, postoperative. Anesthetics, fentanyl: bioavailability. Anesthetic techniques, transmucosal: fentanyl. Pharmacokinetics: fentanyl.)

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ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC) is a novel, noninvasive dosage form of fentanyl used to provide children and adults with sedation, anxiolysis, and analgesia.[1-3] OTFC units consist of a lozenge with a handle and are of uniform size and shape. They are made by dissolving fentanyl citrate in a sucrose solution that is poured into a mold and allowed to harden on a handle. In the mouth, the unit dissolves in saliva: a portion of the fentanyl diffuses across the oral mucosa, and the rest is swallowed and partially absorbed in the stomach and intestine. In theory, oral mucosal absorption of fentanyl should be rapid, since the molecular size of fentanyl is small and the drug is highly lipid-soluble. However, to date, no pharmacokinetic data exist for fentanyl administration using this new delivery system. Therefore, our study was designed to determine the absorption and bioavailability of OTFC in adult volunteers. To characterize gastrointestinal absorption of fentanyl, a similar analysis was performed after some of the same volunteers had swallowed an oral solution of fentanyl citrate.

Materials and Methods

Approval was obtained from the Human Institutional Review Board of the University of Utah Medical Center, and informed written consent was obtained from 12 healthy adult male volunteers. Subjects were nonsmokers, 23–31 yr of age, who deviated no more than 15% from ideal body weight (68–85 kg); they had no history of drug or ethanol abuse and were not taking any pain medications.

In a randomized crossover fashion, subjects were given 15 μg/kg of fentanyl during each 24-h study session either by the iv or by the oral transmucosal route. That is, in the first study session, half of the volunteers were given iv fentanyl, and the other half, OTFC. Eight of the original 12 volunteers returned for a third session, at which time they swallowed an oral solution of fentanyl (hereafter called "oral administration" and "oral fentanyl"). All three sessions were completed within 3–4 months.

Subjects fasted overnight prior to each study session. At the start of each study session, a peripheral 18-G iv catheter was inserted for maintenance fluid administration (lactated Ringer's solution at the rate of 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$), and a 20-G catheter was inserted into the radial artery for blood sampling. Additional monitors included a noninvasive automatic blood pressure cuff, a pulse oximeter and an electrocardiogram.

The three modes of fentanyl delivery were as follows. Intravenous (iv) administration consisted of a continuous infusion at the rate of 150 μg/min until a total of 15 μg/kg was given. For oral transmucosal administration, subjects were instructed to place a 15 μg/kg OTFC unit in the buccal pouch and suck on it, pacing themselves (with instruction from the investigator) so that the unit was consumed in 15 min. For oral administration, a 15-μg/kg OTFC unit was dissolved in sterile water to a total of 10 ml. Volunteers swallowed this solution, rinsed their mouths with two 5-ml aliquots of sterile water, and swallowed the rinsing water.

Finger pulse oximetry was used for continuous monitoring of each subject's hemoglobin oxygen saturation (Sp_{O_2}). Respiratory rate, systolic and diastolic arterial blood pressures, and heart rate were measured and recorded at baseline and just prior to arterial blood sampling. If Sp_{O_2} decreased to less than 90%, subjects were encouraged to take a deep breath. If Sp_{O_2} did not increase to greater than 90% after three prompts, oxygen was administered by nasal cannula at the rate of 3 l/min. If apnea or rigidity occurred, ventilation with 100% oxygen was controlled using a face mask and breathing bag. All adverse reactions were recorded.

Blood Sampling and Fentanyl Analysis

Blood samples (4 ml) were obtained from the arterial catheter at baseline and for 24 h during all three study sessions, at the following intervals. For iv administration, samples were obtained every 2 min during infusion; after infusion, they were obtained every 1 min for 10 min, every 15 min for the 1 h, and then every 2 h for 24 h. Blood samples were obtained every 5 min during OTFC consumption; after consumption, they were obtained every 2 min for 10 min, every 5 min for the next 1 h, and then every 2 h for 24 h. For oral administration, blood samples were obtained every 10 min for 2.5 h after the swallowing of the fentanyl solution, 30 min later, and then every 2 h for 24 h.

All blood samples were injected into preheparinized glass tubes and placed immediately on ice. Plasma was separated from red cells with a refrigerated centrifuge, placed in polypropylene tubes, and frozen at −20° C until analysis for fentanyl.

Plasma fentanyl concentrations were determined by radioimmunoassay using the modified technique described by Schüttler and White.[4] The assay was sensitive to 0.2 ng/ml with a coefficient of variation of 10% at 0.2 ng/ml, 4% at 0.8 ng/ml, and 2% at 1.7 ng/ml.

Pharmacokinetic Analysis

The area under the plasma fentanyl concentration *vs.* time curve after iv, OT, and oral solution administration (AUC_{iv}, AUC_{OTFC}, and AUC_{oral}, respectively) was calculated from the time of administration of fentanyl to the last measurable plasma concentration using the linear trapezoid method.[5] Extrapolation of the AUC from the time of the last measurable fentanyl concentration to infinity was calculated by dividing the last plasma concentration by the first-order rate constant of the terminal phase of the profile. This first-order rate constant was determined using linear regression on the log-transformed plasma fentanyl concentration data from the terminal log-linear phase of the plasma concentration profile. The sum of these two components was the estimate of the total AUC. The terminal elimination half-life of fentanyl was calculated from the first-order rate constant of the terminal phase of the plasma concentration *versus* time profile.

Also calculated were the other following variables: clearance, mean residence time, and volume of distribution of fentanyl at steady state using noncompartmental analysis[6]; clearance as the ratio of the iv fentanyl dose and AUC_{iv}; mean residence time, as the ratio of the area under the first moment curve of iv fentanyl concentration *versus* time data and AUC_{iv}; and volume of distribution at steady state as the product of clearance and mean residence time. The unit disposition function for fentanyl was determined using least-squares deconvolution of the plasma fentanyl concentrations from the iv portion of the study by the dosing function for the iv portion.[7] Deconvolution was done with the constraint that the resultant unit disposition function be a positive, nonincreasing function.

For the OTFC administration portion of the study, the maximum plasma concentration of fentanyl and its time of occurrence were noted from the plasma concentration *versus* time profile. The amount of fentanyl absorbed after OTFC administration was calculated as the product of fentanyl clearance (determined from the iv study) and AUC_{OTFC}. Bioavailability was calculated as the ratio of the amount of fentanyl absorbed to the amount administered. The absorption profile of OTFC was determined using least-squares deconvolution of the plasma concentrations of OTFC by the fentanyl unit disposition function. This deconvolution was performed with the constraint that the resulting absorption profile be a positive function at all time points. The total area under the absorption profile yielded a second estimate of the amount of fentanyl absorbed and hence a second estimate of bioavailability of OTFC. Data obtained from the oral fentanyl portion of the study was analyzed in a manner identical to that of the OTFC portion.

Continuous variables from the OTFC and oral solution portions of the study were compared by paired-sample *t* test and analysis of variance for repeated measures. Only matching data from the eight subjects who completed both OTFC and oral solution portions of the study were used for these comparisons. Differences were significant if $P < 0.05$. Unless otherwise stated, results are presented as mean values ± standard deviations.

TABLE 1. Terminal Elimination of Half-life of Fentanyl (min) Given by Three Routes of Administration

Subject	Intravenous	Oral Transmucosal	Oral Solution
1	402	523	434
2	348	309	497
3	913	450	ND
4	346	ND	410
5	396	691	329
6	423	384	688
7	394	468	ND
8	360	567	420
9	435	182	467
10	602	943	772
Mean* ± SD	425 ± 102	460 ± 313	469 ± 123

ND = not done; see text. *Harmonic mean.

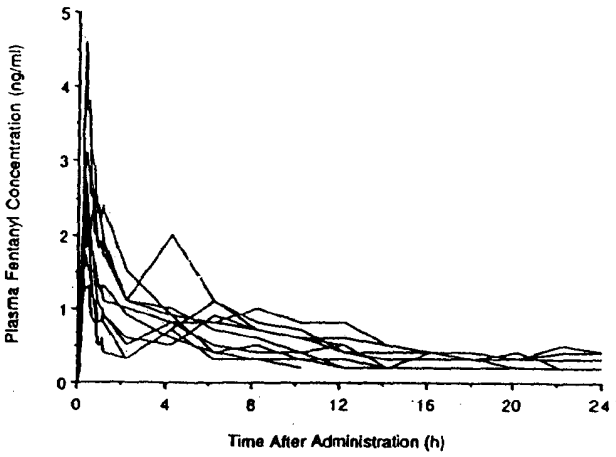

FIG. 2. Measured plasma concentrations of fentanyl for each of ten subjects who consumed OTFC 15 μg/kg.

Results

Twelve subjects completed the iv administration portion of the study, 11 the OTFC section, and 8 the oral solution section. Data from subjects 11 and 12 (iv administration) were included neither in the sample mean nor in the pharmacokinetic analysis, since the iv terminal elimination phase was not well characterized for subject 11 and since there were no matching OTFC data for subject 12 (due to inability to insert the arterial catheter). The mean age and weight of the subjects were 28 ± 2.7 yr and 76 ± 5.4 kg. The mean amount of fentanyl administered was 1,139 ± 85.4 μg. In all subjects consumption of OTFC units was completed in 15 min.

PHARMACOKINETICS

After iv infusion, clearance of fentanyl was 0.67 ± 0.15 l/min; volume of distribution at steady state was 287 ± 79 l; and terminal elimination half-life was 425 ± 102 min (table 1). Figures 1–3 show the plasma concentrations of fentanyl obtained after iv, OTFC, or oral administration, respectively, for individual subjects; figure 4 shows a comparison of the mean data of all three routes of administration. While plasma concentrations of fentanyl are approximately ten times greater after iv administration, there is no difference in terminal elimination after iv, OTFC, or oral administration (fig. 4 and table 1). Table 2 provides individual values for peak plasma concentration of fentanyl and its time of occurrence for both OTFC and oral administration. The peak plasma concentration of fentanyl was greater (3.0 ± 1.0 *vs.* 1.6 ± 0.6 ng/ml, $P = 0.01$) and occurred sooner (22 ± 2.5 *vs.* 101 ± 49 min, $P = 0.003$) after OTFC administration than after oral administration (fig. 5; Table 2). Plasma fentanyl concentrations decreased to below 1.0 ng/ml within 75–135 min after the beginning of OTFC administration (fig. 5).

Figure 6 shows the mean rates of absorption of fentanyl into the systemic circulation after OTFC and oral administration. Peak absorption rate for fentanyl was greater (11.1 ± 4.3 *vs.* 3.6 ± 2.1 μg/min, $P = 0.004$) and occurred sooner (19.0 ± 2.6 *vs.* 87.5 ± 38.1 min, $P = 0.001$) after

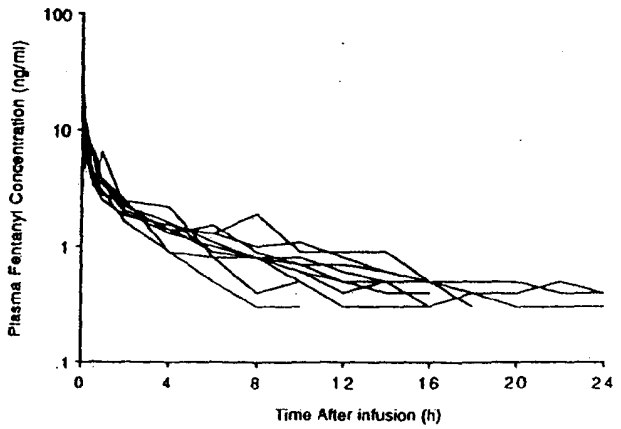

FIG. 1. Measured plasma concentrations of fentanyl for each of ten subjects who received the intravenous fentanyl infusion of 15 μg/kg.

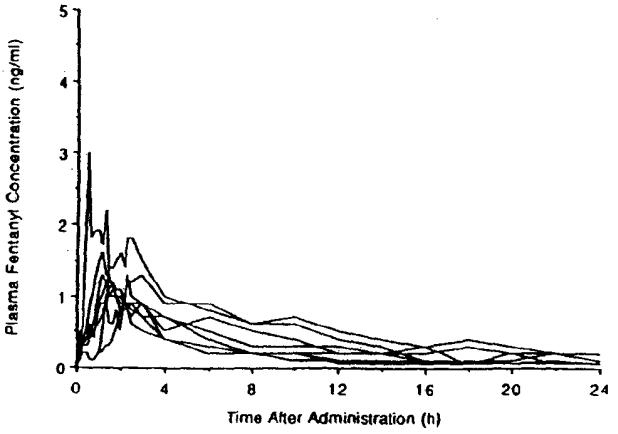

FIG. 3. Measured plasma concentrations of fentanyl for each of eight subjects given orally a solution of fentanyl 15 μg/kg.

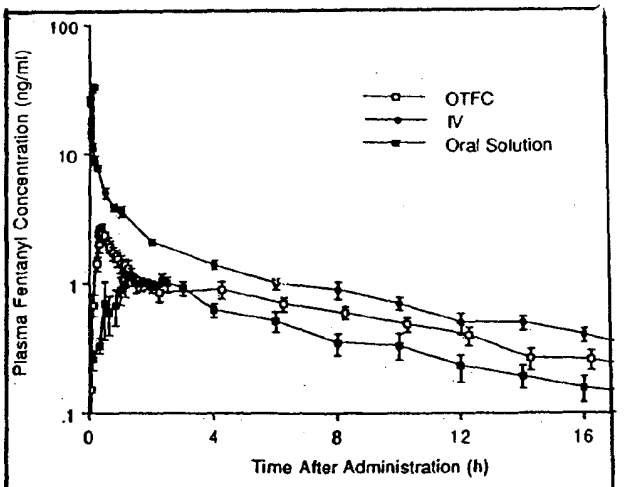

FIG. 4. Plasma concentrations of fentanyl (mean ± SEM) after intravenous (n = 10), OTFC (n = 10), or oral (n = 8) administration of fentanyl 15 μg/kg. Intravenous fentanyl was infused at a rate of 150 μg/kg; OTFC was consumed in 15 min; and the oral solution was swallowed within 10 s.

OTFC administration than after oral administration: it occurred just 4 min after the *completion* of consumption. The absorption rate of fentanyl decreased to below 1.0 μg/min (<10% of the peak) within 75–135 min of the beginning of OTFC administration.

Table 3 shows the bioavailability of OTFC and oral fentanyl, as determined by two methods (dose-normalized AUCs and area under the absorption rate *vs.* time profile). These two methods produced similar results. Mean bioavailability (by the AUC method) was greater after OTFC administration (0.52 ± 0.1) than after oral administration (0.32 ± 0.1) ($P = 0.01$). Figure 7 provides the total amount of fentanyl absorbed into the circulation over 24 h after OTFC and oral administration.

Side Effects

Although 6 of 12 (50%) subjects in the iv section of the study lost consciousness, became rigid, and required positive-pressure ventilation with 100% oxygen to keep Spo_2 greater than 90%, none required paralysis or later had recall of events. The other six subjects needed supplemental oxygen and numerous prompts to breathe in order to keep Spo_2 greater than 90%, but none became rigid or lost consciousness.

There were no significant differences in heart rate and systolic and diastolic blood pressure responses to iv (n = 12), OTFC (n = 11), and oral (n = 8) administration of fentanyl during the entire study. Although changes in respiratory rate after OTFC did not differ over time (0–120 min) from those found after oral administration, mean respiratory rate was significantly less at 10 min (11 ± 4 *vs.* 17 ± 4 breaths per min, $P = 0.005$) and at 20 min (11 ± 4 *vs.* 16 ± 4 breaths per min, $P = 0.05$) after OTFC administration than after oral administration. Table 4 shows the incidence of undesirable side effects after the three modes of fentanyl delivery. Urinary retention (which lasted 6 h) occurred in one subject after oral administration and in none of the subjects after iv or OTFC administration.

Discussion

Until recently, the pharmacologic management of moderate and severe pain has been limited to parenteral administration of opioid analgesics. However, innovative drug delivery devices using alternative routes of administration now are being developed to improve pain management. To understand the safe and effective use of new forms of drug administration such as OTFC, one must understand the biopharmaceutic characteristics of these delivery systems.

With iv administration, the dose is known exactly, and input into the body is instantaneous. Therefore, the rate and extent of drug distribution and elimination can easily be estimated. With non-iv drug administration, however, absorption, distribution, and elimination occur simultaneously. It is not possible to distinguish among the three

TABLE 2. Peak Plasma Concentrations of Fentanyl and Their Time of Occurrence after OTFC and Oral Solution Administration

	C_{max} (ng/ml)		T_{max} (min)	
Subject	OTFC	Oral Solution	OTFC	Oral Solution
1	2.5	1.8	21	140
2	3.1	3.0	24	30
3	4.3	1.3	19	140
4	1.4	ND	21	ND
5	2.6	1.3	25	180
6	2.8	1.6	19	70
7	2.0	ND	30	ND
8	2.7	1.1	24	100
9	4.6	1.2	21	80
10	1.7	1.3	25	70
Mean ± SD	2.8 ± 1.0	16 ± 0.6	23.0 ± 3.4	101.3 ± 48.8

C_{max} = peak plamsa concentration; T_{max} = time of occurrence of C_{max}; ND = not done.

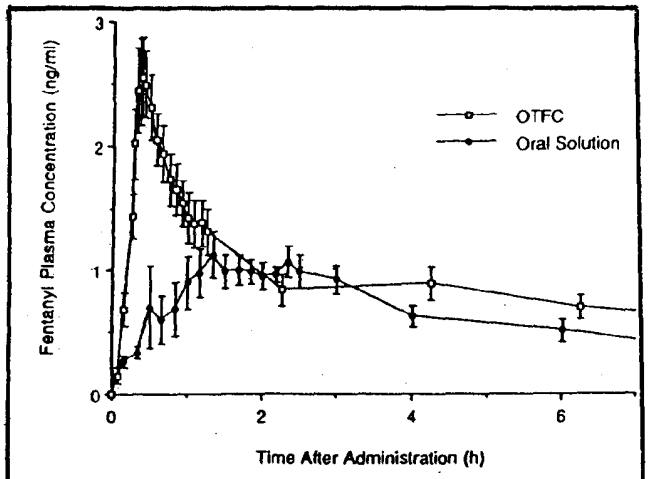

FIG. 5. Plasma concentrations of fentanyl (mean ± SEM) after OTFC or oral administration for the eight subjects who completed these sections of the study. OTFC was consumed in 15 min, and the oral solution was swallowed within 10 s.

processes when examining the curve for plasma concentration of fentanyl *vs.* time. By studying the pharmacokinetics of iv administration on one occasion and the pharmacokinetics of an alternative route of administration on another, it becomes possible to use mathematical approaches (deconvolution) to extract the true profile for absorption from that of distribution and elimination. It is not accurate to estimate absorption using iv and non-iv studies from different individuals (*i.e.*, using previously determined iv population kinetics for the deconvolution of currently determined plasma concentrations after OTFC administration).[8] Instead, it is necessary to use the same individual for both iv and non-iv administrations and to assume that distribution and elimination remain the same between studies. Only by using stable isotope techniques can iv and an alternate route of drug delivery be studied simultaneously in the same individual.

Absorption of fentanyl after oral transmucosal administration first involves entry of the drug into the body through the oral mucosa and then absorption of the fentanyl swallowed in saliva through the gastrointestinal tract. Thus, our study design used the same individual for iv, OTFC, and oral administration to determine and contrast absorption after non-iv routes of administration.

Our pharmacokinetic data from iv studies are comparable to those in the literature, despite the use of different techniques for analyzing the pharmacokinetic data.[9-11] Noncompartmental statistical moment theory does not require that the pharmacokinetic data be fit to a specific one-, two-, or three-compartmental model. The only required assumption is that the pharmacokinetic relationships are linear, *i.e.*, that a change in the dose of drug administered produces a proportional change in plasma concentration. In addition, noncompartmental analysis avoids the problems associated with nonlinear regression and does not force the data to fit preconceived pharmacokinetic models. The results are derived directly from the data rather than from curve "fits" that only approximate the data.

One assumption critical to the analysis of our data is that the distribution and elimination characteristics of fentanyl for an individual subject would not change significantly from study day to study day. Unfortunately, there is no way to know whether this is true, and if not true, to know how much variation would occur from session to session. Although we attempted to minimize the interval between sessions, ethical and practical constraints led to a 3- to 4-month interval for each volunteer's completion of the three-session study. A dose of 15 μg/kg was chosen so that plasma fentanyl concentrations could be followed for 24 h (as was necessary to accurately determine elimination half-life). It is possible that the profound physiologic effects (rigidity and hypercarbia) caused by this iv dose contributed to the inequality of fentanyl disposition between studies.

Our study is the first high-resolution pharmacokinetic study of oral transmucosal and gastrointestinal absorption of fentanyl. Comparison of the plasma fentanyl concentration *versus* time curves for OTFC and oral administration (fig. 5) shows the profound influence oral mucosal absorption plays on the movement of fentanyl into the bloodstream. Peak plasma concentrations of fentanyl after OTFC occurred 86 min before the peak concentrations after oral administration. Furthermore, peak concentrations were twice those after OTFC than after oral administration. This result is important because peak plasma concentrations relate directly to maximum drug effect. Gourlay *et al.*[12] estimated the blood concentrations of fentanyl needed for analgesia after upper or lower ab-

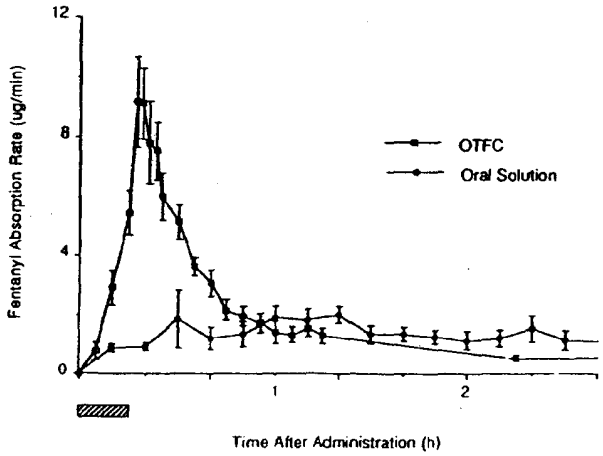

FIG. 6. Absorption rates (mean ± SEM) of fentanyl after OTFC or oral administration for the eight subjects who completed these two studies. The bar represents consumption time (15 min) for OTFC. The oral solution was swallowed within 10 s.

TABLE 3. Bioavailability of Fentanyl After OTFC and Oral Solution Administration as Determined by Two Methods

Subject	Dose-normalized AUCs*		Least-square Deconvolution*	
	OTFC	Oral Solution	OTFC	Oral Solution
1	0.48	0.47	0.44	0.45
2	0.59	0.35	0.54	0.31
3	0.49	ND	0.55	ND
4	0.42	0.25	0.47	0.23
5	0.71	0.35	0.59	0.36
6	0.52	0.42	0.53	0.37
7	0.36	ND	0.34	ND
8	0.44	0.30	0.40	0.28
9	0.37	0.19	0.37	0.17
10	0.63	0.24	0.49	0.26
Mean ± SD	0.50 ± 0.11	0.32 ± 0.10	0.47 ± 0.08	0.31 ± 0.09

ND = not done.

* See text.

dominal surgery. The *minimum* concentration found to relieve postoperative pain ranged from 0.23 to 1.18 ng/ml (mean 0.63 ng/ml).[12] Therefore, an OTFC dose of 15 μg/kg, or approximately 1 mg/70 kg, produced plasma concentrations that were consistently therapeutic for postoperative pain within 15 min of administration. These concentrations lasted for 1–2 h. Thus, an OTFC dose of 15 μg/kg might be useful for management of acute postoperative pain.

Using iv pharmacokinetic data and deconvolution analysis, it is possible to explain the plasma concentration *vs.* time profile discussed above. Absorption of fentanyl is faster and bioavailability greater after OTFC administration than after oral administration (fig. 6). The maximal rate of absorption during and after OTFC administration, approximately 10 μg/min, markedly exceeds the maximal rate of uptake possible from oral administration. Figure 7 demonstrates that the rapid rate of fentanyl absorption after OTFC administration allows approximately 150 μg of fentanyl to be absorbed within 30 min—a dose that, given iv, would be capable of producing moderate analgesia. The overall bioavailability of OTFC (50%) exceeds that of oral fentanyl (30%) because fentanyl that is swallowed undergoes moderate first-pass extraction in the liver. Because fentanyl that is absorbed transmucosally does not undergo this process, more unmetabolized fentanyl enters the systemic circulation.

Most clinical experience with OTFC has involved pediatric patients or those with cancer. Therefore, one must take care when extrapolating our results, obtained in healthy adult men, to these patient populations and to other groups who may have altered fentanyl pharmacokinetics.

Absorption of fentanyl through oral mucosal membranes is complex and involves numerous factors. During consumption of OTFC, the rate of sucking and saliva production (which is affected by the taste and *p*H of the lozenge) influences the dissolution process. Drug-laden saliva is then exposed to the absorptive surfaces of the mouth, including buccal, sublingual, gingival, and tongue mucosae. Although not specifically characterized for fentanyl, drug permeability is generally highest in the sublingual and buccal areas and lowest through the gingiva and tongue.[15] The remaining unabsorbed fentanyl is then swallowed. The amount of saliva immediately swallowed without adequate exposure to mucosal surfaces is a critical factor in overall absorption and probably accounts for much of the interpatient variability associated with OTFC delivery. In general, diffusion though biologic membranes occurs most favorably when a drug is in its nonionized, most lipid-soluble form. Ionization of fentanyl (a weak base, having a *p*Ka of 8.4[14]) depends on environmental *p*H. Higher *p*H favors the unionized form of fentanyl and enhances mucosal penetration. The *p*H in the mouth after OTFC administration results from a combination of saliva (*p*H 6.5–6.9)[15] and dissolved sucrose base (*p*H 5.5–6.0).

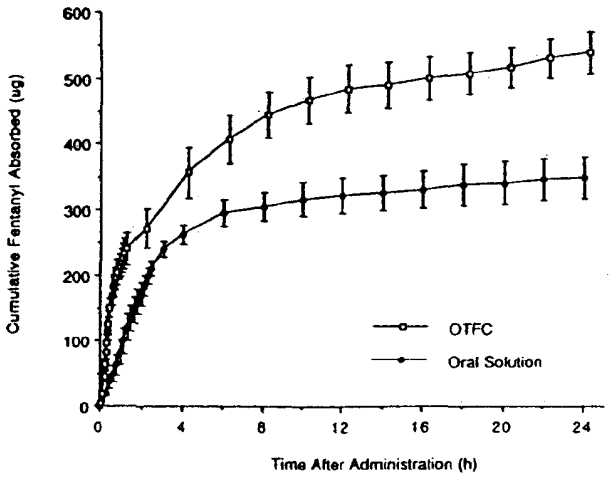

FIG. 7. Cumulative absorption of fentanyl (mean ± SEM) after OTFC or oral administration.

TABLE 4. Side Effects of Fentanyl *via* Three Routes of Administration

	Intravenous (n = 12)	Oral Transmucosal (n = 11)	Oral Solution (n = 8)
Pruritus	10	7	6
Nausea	7	3	3
Emesis	4	3	2

Values shown are the numbers of subjects experiencing each side effect.

Finally, changes in blood and lymph flow to the sites of absorption also influence transport of fentanyl into the systemic circulation.

Transdermal administration is another noninvasive form of fentanyl delivery to which OTFC administration can be compared.[10] Both the skin and oral mucosa are composed largely of stratified squamous epithelium. However, the thick, keratinous, poorly vascularized stratum corneum covering the viable epidermis of the skin impedes the absorption of fentanyl. In contrast, the epidermal lining of the mouth is thin and highly vascularized and thus more readily penetrated by fentanyl. These structural differences may also account for the markedly different values for terminal elimination half-life of fentanyl after OTFC (6.7 h) and transdermal administration (17 h).[10] Apparently, a fentanyl "depot" exists in the stratum corneum of the skin with the use of the transdermal device. However, similarity in the elimination half-life of fentanyl after iv and OTFC administration suggests that a fentanyl depot does not exist in the oral mucosa. Transdermally administered fentanyl is neither degraded by the bacteria of the skin nor susceptible to cutaneous metabolism before reaching the systemic circulation.[10] Unfortunately, the propensity for bacteria of the mouth and oral mucosa to metabolize fentanyl could not be evaluated in this study, since the total amount of fentanyl exposed to the oral mucosa was not known.

The incidence and severity of side effects in this study can be explained by comparing the rates of fentanyl input into the body and the peak blood concentrations attained with each route of administration. Muscular rigidity occurred only after iv administration. Likewise, all subjects became apneic immediately after iv infusion, whereas respiration was slowed just moderately 10–20 min after OTFC administration. Respiratory rate did not change from baseline after oral administration.

In conclusion, our data demonstrate that OTFC administration yields plasma concentrations that are higher and more rapidly attained than those after oral administration. Correspondingly, bioavailability after OTFC administration is greater than that after oral administration. This result provides compelling evidence that fentanyl from OTFC oral passes by mucosal transport directly into the systemic circulation without undergoing first-pass metabolism in the liver. Furthermore, since fentanyl elimination was not longer after OTFC than after iv administration, no fentanyl depot appears to exist in the oral mucosa.

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Oral Transmucosal Fentanyl Citrate: Randomized, Double-Blinded, Placebo-Controlled Trial for Treatment of Breakthrough Pain in Cancer Patients

*John T. Farrar, James Cleary, Richard Rauck, Michael Busch, Earl Nordbrock**

Background: **Patients with cancer frequently experience episodes of acute pain, i.e., breakthrough pain, superimposed on their chronic pain. Breakthrough pain is usually treated with short-acting oral opioids, most of which provide some relief after 15–20 minutes, with peak effects after 30–45 minutes. Oral transmucosal fentanyl citrate (OTFC), a unique formulation of the opioid fentanyl, has been shown to provide meaningful pain relief within 5 minutes in patients following surgery. We conducted a multicenter, randomized, double-blinded, placebo-controlled trial of OTFC for cancer-related breakthrough pain.** ***Methods:*** **Patients who were 18 years of age or older, receiving the equivalent of at least 60 mg oral morphine or at least 50 µg transdermal fentanyl per day for chronic cancer-related pain, and experiencing at least one episode of breakthrough pain per day were studied. After titration to an effective OTFC dose, subjects were given 10 randomly ordered treatment units (seven OTFC units and three placebo units) in the form of identical lozenges. If acceptable pain relief was not achieved within 30 minutes, subjects were instructed to take their previous breakthrough pain medication (i.e., rescue medication). Pain intensity, pain relief, and use of rescue medication were evaluated at 15-minute intervals over a 60-minute period.** ***Results:*** **Eighty-nine of 92 patients who received the randomized treatment were assessable (i.e., treated with at least one unit of OTFC and one unit of placebo). OTFC produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided $P<.0001$). Episodes treated with placebo required the use of rescue medication more often than episodes treated with OTFC (34% versus 15%; relative risk = 2.27; 95% confidence interval = 1.51–3.26; two-sided $P<.0001$).** ***Conclusions:*** **OTFC appears effective in the treatment of cancer-related breakthrough pain. [J Natl Cancer Inst 1998;90:611–6]**

In addition to persistent pain *(1)*, patients with cancer frequently experience superimposed intermittent episodes of acute pain, which is commonly referred to as incident or breakthrough pain *(2)*. These transient and often intense flares of pain can be a particularly troublesome feature of chronic cancer-related pain *(3)*. Although few studies *(2,4)* have been conducted to examine this problem specifically, recent reports indicate that breakthrough cancer pain, severe to excruciating in intensity, occurs in up to 65% of patients with cancer and is frequently undertreated.

The current standard of care for treating cancer pain is to provide a sustained-release preparation that controls the chronic, persistent pain and a rapid, relatively short-acting analgesic that relieves the breakthrough pain without lingering so long as to cause somnolence once the painful episode has subsided. Although data demonstrating efficacy have not been published, the mainstays of breakthrough pain therapy are short-acting oral opioids that are generally believed to have an onset of 15–20 minutes and a peak effect after 30–45 minutes.

Oral transmucosal fentanyl citrate (OTFC) is a unique formulation in which fentanyl, a potent and short-acting opioid that binds primarily to the morphine (mu)

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See "Notes" following "References."

receptor, is incorporated into a sweetened lozenge attached to a stick. The fentanyl is absorbed through the oral mucosa as the lozenge dissolves in the mouth *(5)*. OTFC has been shown to have properties of onset and peak activity similar to those of intravenous morphine *(6)*. Of the total available dose, 25% is absorbed transmucosally over a 15-minute period, and an additional 25% is absorbed through the gastric mucosa during the next 90 minutes *(7)*. The onset of meaningful relief has been shown to occur as quickly as 5 minutes in patients with postoperative pain *(6)*. The pharmacokinetics of OTFC in patients with cancer were evaluated in another study *(8)*.

OTFC has been useful for the management of breakthrough pain in patients with cancer in two open-label reports *(9,10)*.

In this report, we present data from a multicenter, randomized, placebo-controlled, double-blinded clinical trial to determine whether patients with breakthrough cancer pain obtain clinically important pain control more often with the active fentanyl product than with an identical placebo delivery system alone.

Patients and Methods

Patients with cancer who had relatively stable pain and who were 18 years of age or older were recruited from 23 different community and academic cancer centers (*see* "Appendix: Study Group List"). This study was approved by the institutional review board at each study site, and all patients gave written, informed consent prior to participation. Most patients were known to the investigators, but a few were referred by the local physicians' network specifically for this trial. All types and stages of cancer were acceptable, provided the patients reported sufficient pain to require at least the equivalent of 60 mg/day oral morphine or at least 50 μg/hour transdermal fentanyl and had at least one episode of breakthrough pain per day for which they took additional opioids. Patients were provided with free study medication but were not otherwise compensated for their participation.

A thorough medical history was recorded, and a physical examination was carried out to collect demographic data and to ensure that there was no history of psychiatric disease or of drug abuse as well as no evidence of oral, hepatic, renal, or cognitive disease that would prevent participation in the study. All study subjects were started on 200 μg OTFC (developed by Anesta Corp., Salt Lake City, UT, and distributed by Abbott Laboratories, Abbott Park, IL) as a replacement for their prescribed breakthrough medication as part of an open-label dose titration. Subjects were taught how to consume the total dose within 15 minutes and were instructed that, if they did not perceive adequate pain relief after 30 minutes, they were allowed to take a dose of their usual rescue medication (i.e., their previous breakthrough pain medication). For each episode of breakthrough pain treated with an OTFC unit, all subjects were taught how to fill out the medication diary, including the time, the date, and product information (i.e., placing the peel-off sticker from the individual dose package into the diary). The validated pain scales *(11,12)* used in this study included pain intensity (0 = no pain → 10 = worst pain), pain relief (0 = none → 4 = complete), and global performance evaluation (0 = poor → 4 = excellent). Information on whether the patient decided to take additional medication for the relief of pain for each episode (yes or no) was also collected as a novel outcome with clear clinical importance. Since previous studies on dosing *(5,8,9)* were not able to define a consistent analgesic-equivalency table for conversion of other opioid rescue medications to the appropriate OTFC dose, all subjects were started on the lowest dose (200 μg) and maintained close contact with study staff to ensure a safe titration. They were then titrated to an effective dose up to the maximum available dose (1600 μg) over a 2-week period. An effective dose was defined as the dose required to treat most episodes of breakthrough pain with a single OTFC unit. Subjects were instructed to return their diaries, used OTFC containers, and unused doses at each clinic visit. The diaries were reviewed by a research nurse in the presence of the subject to ensure accurate and complete data entry.

All subjects who were able to achieve adequate relief with OTFC were advanced to the randomized, double-blinded phase, which was designed as a 10-period crossover. In this phase, each subject was given a box of 10 sequentially numbered units. Of the 10 units, seven contained fentanyl at the same dose found effective for that patient in the titration phase, and three were placebo units. So that we could maintain study blinding, the placebo doses were formulated identically (i.e., color, taste, and texture) and packaged identically to the active drug. The ordering of the placebos and active units was random for each patient, with one placebo in the first three units, another in the second three units, and one in the last four units, but always with a separation of at least one active dose between two placebos (for ethical reasons). A sealed key was provided with each study box for emergency use, but none was needed during the study. One third of the patients had placebo as a first dose, one third had it as a second dose, and one third had it as a third dose. Of the 804 episodes of pain treated, 247 (30.7%) were treated with placebo and 557 (69.3%) were treated with active drug.

Subjects were instructed to use the units in sequential order, with a minimum of 2 hours between episodes treated with OTFC, and to record the unit number for each one used by placing the peel-off sticker from the unit in the appropriate box in their study diary. If pain relief was not adequate within 30 minutes, patients were encouraged to take a dose of their previous non-study breakthrough pain medication. *A priori* criteria were established to deal with protocol violations, including an interval of less than 2 hours between doses of OTFC, variation of more than 10 minutes in any of the four required 15-minute recordings following the consumption of a unit (i.e., at 15, 30, 45, and 60 minutes), incomplete consumption of a unit, treatment of a pain different from that originally designated, and incomplete records. These rules were applied to each treated episode before the blinding was broken. For the primary analysis (but not for the intention-to-treat analysis), protocol violations were excluded. After completing the randomized phase, all patients were given the option to continue the use of OTFC for as long as they found the product effective for their breakthrough pain.

The original protocol specified the primary outcomes as the sum of the pain intensity differences (i.e., the area under the curve of the pain intensity differences) and the total pain relief (i.e., the area under the curve of the pain relief values), calculated after the exclusion of all episodes found to have significant protocol violations (74 episodes). However, since both of these measures require imputation of data, an intention-to-treat analysis is presented first and includes all data from all patients who took at least one active and one placebo dose (801 episodes). The average pain intensity difference and pain relief are reported at each time point. Since individuals were allowed to take an additional dose of their previous medication after 30 minutes, not all subjects had 45-minute and 60-minute values. The total number of assessable subjects at each time point is presented in the "Results" section. To calculate the sum of the pain intensity differences and the total pain relief, we used the conservative last occurrence carry forward method to impute missing values for the 45-minute and 60-minute time periods in subjects who decided to take additional rescue medication before the full 60-minute recording period had elapsed. The sum of the pain intensity differences is calculated by subtracting the pain intensity at any point from the baseline (i.e., 0 minutes) and cumulatively adding up these values over the four measurement times of the study (i.e., 15, 30, 45, and 60 minutes) *(13)*. The total pain relief is calculated by cumulatively adding the pain relief measured at each time period *(13)*.

The mean values of the episodes treated with active drug and the episodes treated with placebo were assessed for each time period by use of a paired *t* test. Since each patient had multiple exposures to both placebo and active drug, generalized evaluation equations were used to account for the lack of independence of the episode data by clustering the episode values for each subject to provide an accurate *P* value for clustered data *(14,15)*. As noted above, all patients who consumed at least one active and one placebo unit were included in the analysis. The same method was used to perform a secondary analysis of the subjects' reported satisfaction with the treatment and whether they took additional rescue medication. Baseline subject characteristics and side effects are reported descriptively. All statistical analyses were performed with the use of SAS (version 6.01; SAS Institute, Cary, NC) and STATA (version 5.p; STATA Corporation, College Station, TX) software. All reported *P* values are two-sided.

Results

Of the 130 patients originally recruited, 93 completed the open-label titration phase and 37 did not. The primary reasons for not completing the open-label

phase were patient choice (n = 15), advancing cancer limiting the patient's ability to take the drug (n = 12), and specific side effects (n = 10). The specific side effects were nausea/vomiting (n = 6), mental status changes (n = 2), and dyspnea (n = 2). Of the two patients withdrawn for dyspnea, reported as possibly related to the OTFC, one had three mild episodes associated with anxiety in addition to a known history of anxiety-related dyspnea, and the other had lung cancer, chronic obstructive pulmonary disease, and pulmonary emboli. Of the 15 who chose not to continue, four reported that their breakthrough pain spontaneously ceased or substantially decreased, four preferred their previous medication, four were not able to complete the diaries successfully, one was lost to follow-up, and two did not specify a reason.

Of the 93 patients who achieved adequate pain relief with OTFC and were eligible for the randomized, double-blinded phase, 92 agreed to participate. Three of these patients took only one unit (placebo, n = 2; OTFC, n = 1) before dropping out, which left 89 patients in the intention-to-treat analysis. In all, 20 patients did not complete the full 10 doses of the double-blinded phase. Eight of these 20 patients completed four doses or fewer, six completed five doses, four completed six doses, and two completed seven doses, with the remaining 72 patients completing all 10 doses. Of those not completing all 10 doses, 10 did not complete the randomized phase in the required 14 days, six had progression of their cancer, two developed nausea/vomiting or itching, and two chose to discontinue for unspecified reasons. Given the crossover design, all patients served as their own controls.

Table 1 displays demographic data for all 92 patients who chose to participate in the randomized, double-blinded phase, with the primary cancer diagnosis and the type of pain indicated. Overall, there was no statistically significant difference in any demographic variable or type of tumor between those who completed the randomized phase and those who did not. In addition, the majority of the patients were taking oral morphine (68% [n = 63]; dose range, 30–600 mg per day) or using the fentanyl patch (23% [n = 21]; dose range, 50–225 μg per hour) as their around-the-clock medication. The rescue medication replaced by OTFC (and the percentage of patients affected) included oxycodone (37%), morphine (30%), hydrocodone (13%), hydromorphone (12%), and other medications (8%).

Table 1. Characteristics of all patients who participated in the randomized, double-blinded phase of the trial of oral transmucosal fentanyl citrate for cancer-related breakthrough pain

Variable*	Completed double-blinded phase	Did not complete double-blinded phase	Total
No. of patients	72	20	92
Sex			
No. of females (%)	39 (54)	12 (60)	51 (55)
No. of males (%)	33 (46)	8 (40)	41 (45)
Age, y			
Mean ± SD	53 ± 11	57 ± 15	54 ± 12
Range	27–77	29–84	27–84
Height, cm			
Mean ± SD	169 ± 10	167 ± 11	169 ± 10
Range	150–193	142–188	142–193
Weight, kg			
Mean ± SD	71 ± 21	66 ± 13	70 ± 20
Range	42–128	40–91	40–129
Race			
No. black (%)	3 (4)	2 (10)	5 (5)
No. Asian (%)	1 (1)	0 (0)	1 (1)
No. white (%)	68 (94)	18 (90)	86 (93)
Cancer type			
No. breast (%)	18 (25)	3 (15)	21 (23)
No. lung (%)	14 (19)	3 (15)	17 (18)
No. colon/rectal (%)	11 (15)	1 (5)	12 (13)
No. uterine (%)	6 (8)	1 (5)	7 (8)
No. other—solid tumor (%)	14 (19)	9 (45)	23 (25)
No. other—hematologic (%)	9 (13)	3 (15)	12 (13)
Pain type			
No. somatic (%)	38 (53)	10 (50)	48 (52)
No. visceral (%)	22 (31)	7 (35)	29 (32)
No. neuropathic (%)	11 (15)	2 (10)	13 (14)
No. unknown (%)	1 (1)	1 (5)	2 (2)

*SD = standard deviation.

The primary comparison of the pain intensity differences and pain relief in an intention-to-treat analysis is shown in Fig. 1. A comparison of the primary outcome analyses for pain intensity differences and pain relief, excluding patients with protocol violations, is shown in Fig. 2. Eighty-six patients were included in the latter efficacy comparisons; six patients were not included because of protocol violations. The 86 patients generated assessable data from 730 episodes of pain. For all time periods, statistically significant differences ($P<.0001$) were seen between episodes treated with OTFC and episodes treated with placebo. The mean global performance evaluation scales were 1.98 for OTFC and 1.19 for placebo ($P<.0001$). In addition, subjects required significantly more additional rescue medication for breakthrough pain episodes treated with placebo than for episodes treated with the active drug (34% versus 15%; relative risk = 2.27; 95% confidence interval = 1.51–3.26; $P<.0001$). Specifically, patients using placebo were more than twice as likely to require an additional rescue dose as were those who used the active agent. Of the original 92 patients, 74 chose to continue to treat their breakthrough pain with OTFC following the randomized clinical trial. No specific subgroup could be identified that was more or less responsive to OTFC.

Table 2 lists the primary opioid-related adverse events reported for all 130 patients initially enrolled in the trial. Most of the adverse events that occurred in the study were reported by the site investigator as likely due to other treatments or to the cancer itself, as would be expected in patients with cancer. The more frequent opioid-related adverse events reported as possibly related to OTFC were dizziness (17%), nausea (14%), somnolence (8%), constipation (5%), asthenia (5%), confusion (4%), vomiting (3%), and pruritus (3%).

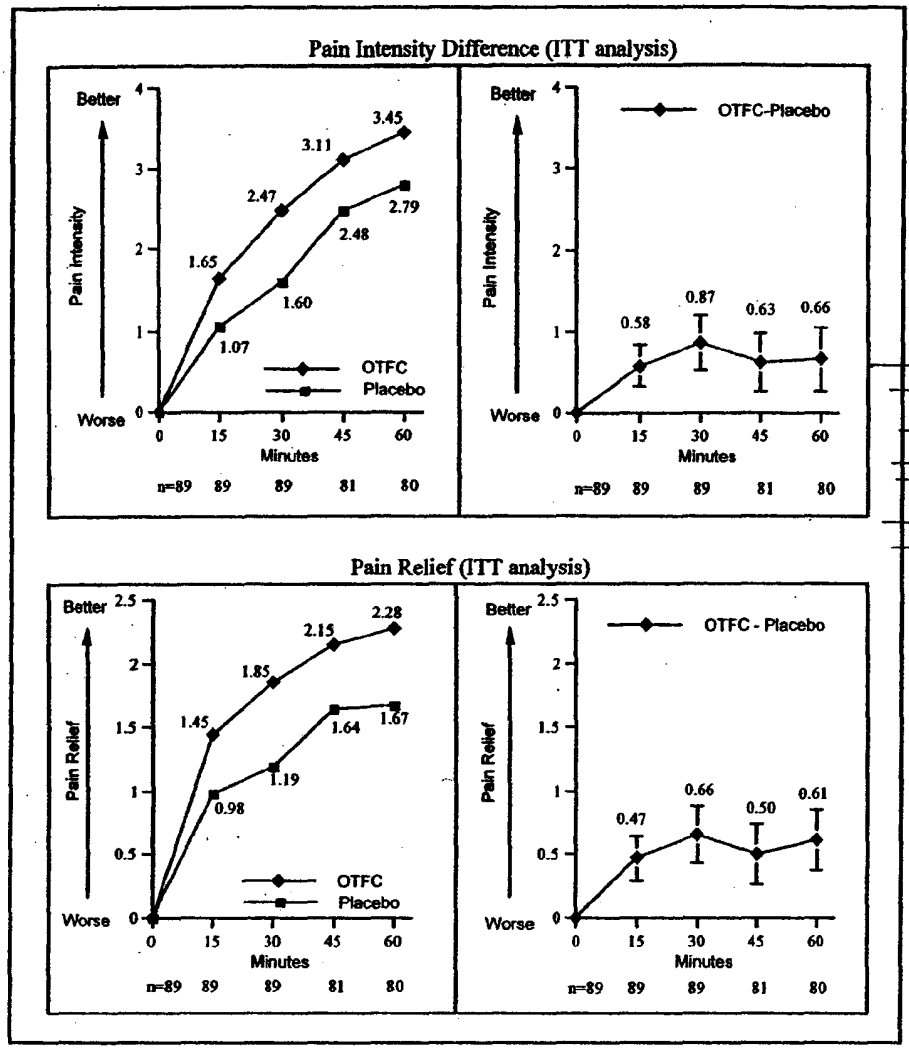

Fig. 1. Intention-to-treat (ITT) analysis of pain intensity differences and pain relief. All patients who entered the double-blinded phase of the trial and who received both oral transmucosal fentanyl citrate (OTFC) and placebo were included. Data were not available for all patients at all time periods. Ninety-five percent confidence intervals are shown for the OTFC minus placebo (i.e., OFTC – Placebo) values for this paired analysis. *See* text for additional details.

Discussion

Pain remains a substantial problem for most patients with cancer. Although the primary impediment to good care worldwide is the inadequate use of currently available pain medications, one of the more difficult aspects of pain treatment has been breakthrough or incident-related pain *(1)*. Even in patients with well-controlled chronic components to their pain, the intermittent pain associated with daily activity or movement can be disabling. This type of pain usually begins relatively acutely and can be quite severe, especially in patients with musculoskeletal metastasis. In one 3-month survey *(2)* of 63 patients with cancer, 41 (65%) reported one or more episodes per day of transient flares of severe or excruciating pain with an overall duration of 1–240 minutes and a median duration of 30 minutes. The pathophysiology of the pain was attributed approximately equally to somatic, neuropathic, visceral, and mixed causes, although the accuracy of such diagnoses is hard to determine *(2)*. The limited literature that exists suggests that the best treatment should consist of a fast-acting drug that has a relatively short half-life, so that the effects of the medication resolve as the pain abates. The usual dose for each episode of pain is 10%–15% of the total 24-hour around-the-clock dose taken at the onset of pain or just before predictable episodes, such as moving a patient with a broken bone. To date, we have been limited to oral (convenient but relatively slow), rectal (relatively slow and inconvenient for frequent use), or parenteral (more rapid but inconvenient and costly) treatments. The transmucosal route is convenient and has a rapid onset, representing an important addition to the potential therapeutic options.

There are several important aspects of this study. The first is that OTFC was found to be statistically significantly better than the placebo in every analysis completed, looking at the changes in the mean values of pain intensity, pain relief, and global performance as well as in the proportion of pain episodes for which subjects required an additional rescue medication (i.e., clinically important change). Therefore, this new delivery system is highly effective in treating episodes of breakthrough pain in patients with cancer. Our study did not show that any specific cancer type or disease pattern was more or less susceptible, but the study was not powered for subgroup analyses; thus, the final answer to this question remains to be resolved.

Second, when properly used in patients who are tolerant to opioids, OTFC has relatively few important side effects. Despite the relatively high doses of fentanyl used, there were no serious events, such as respiratory depression or severe somnolence, attributed to OTFC. However, the dose of fentanyl citrate is large enough that there may be concern about respiratory depression in the opioid-naive patient.

Third, although patients on higher doses of original rescue medication generally required larger doses of OTFC, this relationship was not consistent enough to determine a reliable equivalency ratio, perhaps because rapid absorption changes the pharmacodynamics of treatment.

Fourth, the trial incorporated a number of design advantages and features that were developed specifically for this study. This unique combination of features can be applied to future trials of medications that have rapid onset and potential efficacy in the treatment of breakthrough or acute pain. Specifically, the titration run-in period clearly defines a potentially responsive group of patients, while it also provides invaluable information about patients who may not benefit as much from the therapy. The use of a group of randomly ordered active and placebo medi-

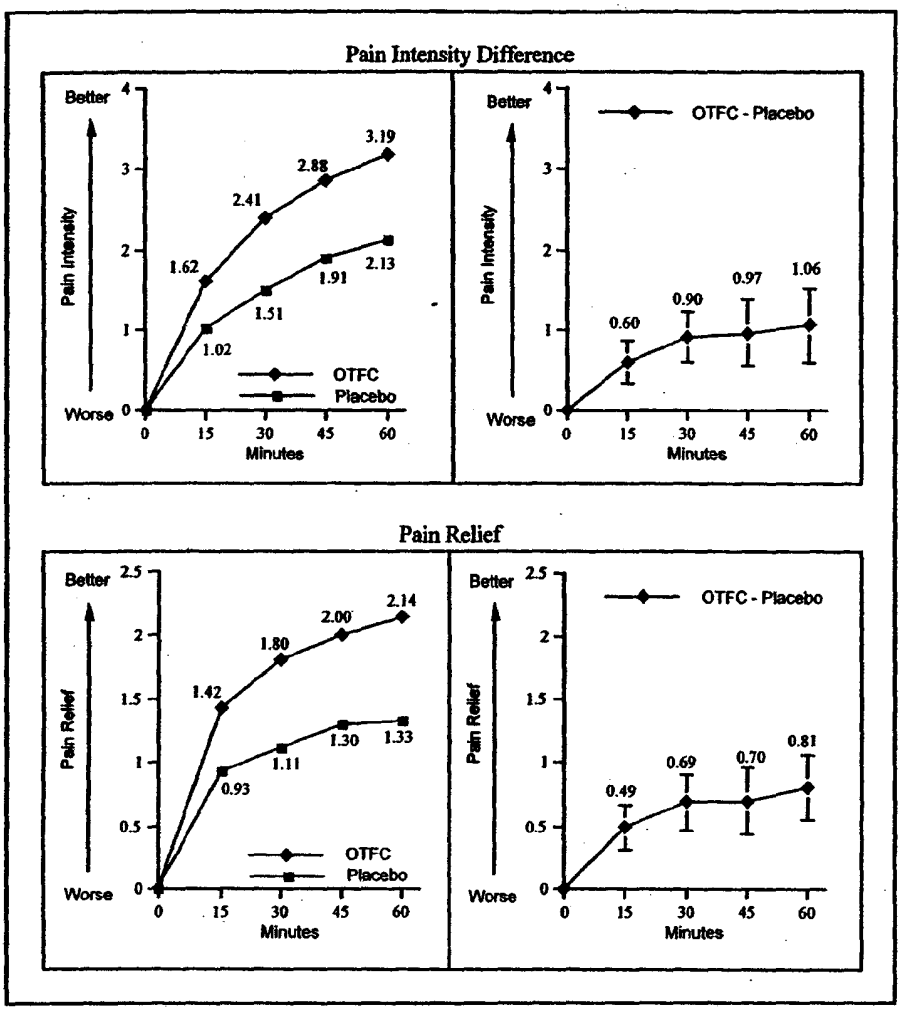

Fig. 2. Primary outcome analyses for pain intensity differences and pain relief. After exclusion of individuals with procedural violations and use of the last occurrence carry forward method to imput missing values, data from 86 patients who entered the double-blinded phase of the trial and received both oral transmucosal fentanyl citrate (OTFC) and placebo were included in the analyses. Ninety-five percent confidence intervals are shown for the OTFC minus placebo (i.e., OTFC – Placebo) values for this paired analysis.

Table 2. Primary opioid-related adverse events for all 130 patients initially enrolled in the trial of oral transmucosal fentanyl citrate (OTFC) for cancer-related breakthrough pain

Typical adverse events*	No. of patients (%)
Dizziness	22 (17)
Nausea	18 (14)
Somnolence	11 (8)
Constipation	7 (5)
Asthenia	6 (5)
Confusion	5 (4)
Vomiting	4 (3)
Pruritus	4 (3)

*Only adverse events that were considered by the investigator to be at least possibly related to the study drug and that occurred on days when an OTFC unit was used are included.

cations for the trial portion of the study, along with a short waiting period before the use of additional rescue medication if needed, provides an ethical way to incorporate placebo controls into an efficacy trial. Given the significant advantages of a placebo control group and the clear ethical issues surrounding the administration of a placebo to sick patients, this feature is important. The frequent measurement of several pain-related scales (especially the measure of those who required additional rescue medications for individual episodes of breakthrough pain) adds additional validity to the results. This measure is clearly different from the more standard time-to-next-rescue response, which incorporates both initial activity and length of effect in a way that can introduce a level of ambiguity into the analysis.

Fifth, some of the subgroup analyses provide interesting hypotheses for future consideration and confirmation. One is that, of the 92 subjects in the randomized phase of the trial, 13 (14%) were reported to have a substantial component of neuropathic pain, which is usually considered to be only partially responsive to opioid therapy *(16)*. Despite this fact, 11 (85%) of the 13 reported clinically important relief with OTFC in the first phase of the study. This result emphasizes the considerable variation in our ability to diagnose and treat different types of pain and is consistent with the idea that most cancer patients have a mixed pain syndrome *(16)*. Our finding suggests that we should not withhold OTFC therapy simply because a patient is thought to have a predominantly neuropathic pain syndrome.

Sixth, it is interesting that 66% of the episodes treated with placebo did not require an additional dose of medication, which is in the upper range for reported placebo responses *(17)*. However, this rate is completely consistent with the disease process, the type of pain, the patient population, and study design in this trial. It is likely that a large portion of this phenomenon can be explained by the normal course of episodes of breakthrough pain, which are often relatively short-lived and improve spontaneously over a time course similar to that which subjects expect when taking the active drug. An additional portion of these episodes might be explained by a true placebo response in which endogenous opioid production or a neurologic down-regulation response (i.e., pain suppression) makes an important contribution to the improvement of the patient's pain.

The limitations of this study are primarily those common to any randomized clinical trial. Since only patients with cancer and clearly defined breakthrough pain treated with chronic opioids were recruited, the generalization of these results to other populations should be done in a carefully considered manner. This medication had a high degree of safety in this closely monitored and opioid-tolerant population; however, the potential for side effects with inappropriate use implies that considerable caution be used in initiating therapy, especially for patients who are opioid naive. In addition, of the 130

patients initially selected to use this medication, 56 (43%) ultimately did not continue to use OTFC beyond the clinical trial period. This value is consistent with other dosage forms and types of opioids *(18)* used to treat cancer-related pain. A majority of these patients developed problems related to important progression of their disease. However, since patients with cancer are the primary target population for this treatment, careful consideration must be given to those who can benefit the most from this form of therapy. The clear advantages of rapid onset and relatively short duration of action may make this form of medication delivery less appropriate for patients whose breakthrough pain is of longer duration.

In conclusion, the OTFC drug-delivery system described here is a highly efficacious treatment for cancer-related breakthrough pain and shows a large margin of safety in patients on chronic opioid therapy. In view of our results and other published findings *(9)*, the advantages of rapid onset, transmucosal absorption (i.e., no need to swallow), titrateability, ease of use, and acceptance by patients make OTFC ideally suited for this purpose.

Appendix: Study Group List

We would like acknowledge the other members of the Anesta Management of Pain Symptoms (AMPS) study group for their collaborative efforts.

The AMPS study group included the following: Robert Berris, M.D., Rocky Mountain Cancer Centers, Denver, CO; Allen Cohn, M.D., University of Colorado Health Sciences Center, Denver; Robert Ellis, D.O., Madigan Army Medical Center, Tacoma, WA; Janet Gargiulo, M.D., Capital District Hematology/Oncology Associates, Latham, NY; Stuart Grossman, M.D., The Johns Hopkins Oncology Center, Baltimore, MD; Lowell Hart, M.D., Associates in Hematology and Oncology, Fort Meyers, FL; Laurel Herbst, M.D., San Diego Hospice, CA; Howard Homesley, M.D., North Carolina Baptist Hospital/Carolina Gynecologic Oncology, Winston-Salem; Laura Hutchins, M.D., Arkansas Cancer Research Center, Little Rock; K. S. Kumar, M.D., United Professional Center, New Port Richey, FL; Michael Levy, M.D., Fox Chase Cancer Center, Philadelphia, PA; John Marshall, M.D., Vincent T. Lombardi Cancer Center, Washington, DC; Timothy J. Ness, M.D., University of Alabama—Birmingham; Kelly Pendergrass, M.D., Kansas City Internal Medicine, MO; Lee Schwartzberg, M.D., The West Clinic, Memphis, TN; Mark Seligman, M.D., Providence Hospice, Portland, OR; Gregory B. Smith, M.D., SW Regional Cancer Center, Austin, TX; Charles von Gunten, M.D., Northwestern University, Chicago, IL; William H. Whaley, M.D., West Paces Medical Center, Atlanta, GA; Donna Saltzburg Zhukovsky, M.D., The Cleveland Clinic Foundation, OH.

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Notes

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Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study

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Abstract

Oral transmucosal fentanyl citrate (OTFC) is a novel opioid formulation in which the potent synthetic μ-agonist fentanyl is embedded in a sweetened matrix that is dissolved in the mouth. It is undergoing investigation as a treatment for cancer-related breakthrough pain, a prevalent phenomenon defined as a transitory flare of moderate to severe pain that interrupts otherwise controlled persistent pain. There have been no controlled trials of other treatments for this condition. To evaluate the safety and efficacy of ascending doses of OTFC, a novel controlled dose titration methodology was developed that applied blinding and randomization procedures to the evaluation of recurrent pains in the home environment. The study was a multicenter, randomized, double-blind dose titration study in ambulatory cancer patients. The sample comprised adult patients receiving a scheduled oral opioid regimen equivalent to 60–1000 mg oral morphine per day, who were experiencing at least one episode per day of breakthrough pain and had achieved at least partial relief of this pain by use of an oral opioid rescue dose. After collection of 2 days of baseline data concerning the efficacy of the usual rescue drug, patients were randomly treated with either 200 or 400 μg OTFC unit doses in double-blind fashion. Up to two breakthrough pains each day could be treated with up to four OTFC unit doses per pain. OTFC in unit doses containing 200, 400, 600, 800, 1200 or 1600 μg of fentanyl citrate were available for the study. The unit dose was titrated upward in steps until the patient had 2 consecutive days on which breakthrough pain could be treated with the single unit dose, titration was ineffective at a 1600 μg unit dose, or 20 days elapsed. To maintain the double-blind, orders to titrate up were ignored one-third of the time according to a pre-defined randomization schedule accessible only to an unblinded study pharmacist. Main outcome measures included, numeric or categorical measures of pain intensity, pain relief, and global assessment of drug performance. Dose response relationships were found suggesting that the methodology was sensitive to opioid effects. Seventy-four percent of patients were successfully titrated. There was no relationship between the total daily dose of the fixed schedule opioid regimen and the dose of OTFC required to manage the breakthrough pain. Although the study was not designed to provide a definitive comparison between OTFC and the usual rescue drug, exploratory analyses found that OTFC provided significantly greater analgesic effect at 15, 30 and 60 min, and a more rapid onset of effect, than the usual rescue drug. Adverse effects of the OTFC were typically opioid-related, specifically somnolence, nausea and dizziness. Very few adverse events were severe or serious. This study demonstrated the feasibility of controlled trial methodology in studies of breakthrough pain. OTFC appears to be a safe and effective therapy for breakthrough pain, and dose titration can usually identify a unit dose capable of providing adequate analgesia. If the lack of a relationship between the effective OTFC dose and fixed schedule opioid regimen is confirmed, dose titration may be needed in the clinical use of this formulation. Further investigation of OTFC as a specific treatment for breakthrough pain is warranted.

Keywords: Oral transmucosal fentanyl citrate; Pain; Cancer

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1. Introduction

Pain related to medical illnesses, such as cancer, typically fluctuates, and patients often report the experience of transient flares. When these transient flares of pain are clinically significant and interrupt a background pain that is otherwise

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controlled and tolerated, they are commonly described as 'breakthrough pains.' Breakthrough pains that are precipitated by a voluntary action, such as movement, are often labeled 'incident' pains. In the cancer setting, breakthrough or incident pain usually implies a moderate to severe transitory pain that punctuates a persistent background pain that is generally well controlled by opioid therapy.

Breakthrough pain is a challenging clinical phenomenon. The prevalence of breakthrough pain in a prospective survey of inpatients with cancer pain was 64% (Portenoy and Hagen, 1990) and surveys indicate that the likelihood of a satisfactory response to opioid therapy is lower among those who report this type of pain than those who do not (Mercadante et al., 1992; Bruera et al., 1995). Clinicians commonly observe a strong association between physical and psychosocial impairments, and either the frequency or intensity of these transient pains.

The potential for adverse consequences associated with breakthrough pain has been the impetus for the development of specific therapeutic strategies. In those populations treated with long-term opioid therapy, the most common approach is the co-administration of a supplemental short-acting analgesic 'as needed,' along with the scheduled long-acting opioid regimen. Guidelines for cancer pain management now include instructions for the use of such a supplemental opioid analgesic (World Health Organization, 1990; American Pain Society, 1992; Jacox et al., 1994), and the term 'rescue dose' is widely applied to describe this approach. Based on clinical observations, the selection of rescue drugs typically focuses on pure μ-opioid agonists with relatively short half-lives and time-action profiles, characterized by a rapid onset, early peak effect and a duration long enough to treat most breakthrough pains. In the cancer population, morphine sulfate, oxycodone and hydromorphone are commonly used for this purpose.

Oral transmucosal fentanyl citrate (OTFC) is currently undergoing investigation as a new treatment for breakthrough pain. In this formulation, the potent synthetic opioid, fentanyl, is incorporated into a sweetened matrix that is dissolved in the mouth, allowing rapid absorption of part of the dose directly through the buccal mucosa (Stanley et al., 1989; Streisand et al., 1991). Currently approved by the United States Food and Drug Administration for anesthetic premedication and conscious sedation in monitored settings, OTFC has been anecdotally reported to be an effective therapy for cancer-related breakthrough pain (Fine et al., 1991).

The systematic investigation of a new opioid formulation for breakthrough pain is unique. In the absence of previous controlled clinical trials of treatments for breakthrough pain, new methodologies were developed to accomplish this goal. A recent study of OTFC demonstrated the feasibility of a randomized, placebo-controlled, multiple cross-over design (Farrar et al., 1998). The present study applied a novel controlled dose titration methodology to evaluate the safety and efficacy of ascending doses of OTFC as specific therapy for breakthrough pain in cancer patients receiving varied scheduled oral opioid regimens for chronic cancer-related pain. This methodology incorporated blinding and randomization procedures into the evaluation of recurrent pains in the home environment.

2. Methods and materials

This multicenter study evaluated the effects on breakthrough pain produced by ascending doses of OTFC, using random assignment and double-blind drug administration to ensure that the patients and study staff were unaware of the actual dose administered as dose titration ensued. The study was approved by the Institutional Review Boards at each site and all patients gave written consent prior to participation.

2.1. Study population

Adult patients with cancer-related pain were eligible for the study if they (1) were receiving a scheduled oral opioid regimen equivalent to 60–1000 mg oral morphine per day (2) had experienced at least one episode per day of breakthrough pain between 0700 and 1600 h on the 3 days immediately preceding screening, and (3) had achieved at least partial relief of this breakthrough pain by the use of an oral opioid rescue dose. Breakthrough pain was defined as a transitory flare of pain to moderate, severe or excruciating intensity that occurred on a background of chronic pain that was maintained at moderate intensity or less by the fixed schedule opioid regimen. If patients had more than one type of breakthrough pain or had breakthrough pain in more than one location, they were asked to identify one pain as a 'target' breakthrough pain for the study. A standard relative potency table (Jacox et al., 1994) was used to determine the morphine equivalent dose for patients who were receiving an opioid other than morphine.

Patients were excluded from the study if they had a recent history of substance abuse, neurologic or psychiatric impairment sufficient to compromise data collection, any major organ impairment that could increase the risk of supplemental opioids for treating breakthrough pain, or any recent therapy that could potentially alter pain or response to analgesics during the study. Specific exclusion criteria included renal or hepatic function tests greater than three times the upper limit of normal, treatment with strontium-89 within 60 days, and treatment with radiotherapy to a painful site within 30 days prior to the study. Patients who had moderate to severe oral mucositis were also excluded.

2.2. Procedures

Patients who remained eligible following screening proceeded to the two phases of the study: (1) opioid dose

stabilization and baseline data, and (2) OTFC dose titration.

2.2.1. Opioid dose stabilization and baseline data

Baseline data concerning the performance of the patient's usual rescue drug were collected on 2 consecutive days during a period of stable dosing. 'Stable' dosing was defined as at least 3 consecutive days during which the scheduled opioid regimen yielded an average daily pain of moderate severity or less, tolerable opioid side effects, and the need for four or fewer rescue doses. If patients had a history of stable dosing for at least 3 consecutive days prior to screening, baseline data collection about the performance of the usual rescue drug was allowed to proceed immediately after screening. Patients who did not meet the criteria for a stable opioid regimen at the time of screening underwent adjustment of the regimen using a standardized procedure based on widely accepted guidelines for the management of cancer pain (American Pain Society, 1992; Jacox et al., 1994; Levy, 1996). This stabilization period, which could continue for as long as 1 month, was stopped when the criteria for stable dosing were achieved for 3 consecutive days. After stable dosing was achieved, the patients collected baseline data for 2 consecutive days. Patients were allowed 5 working days to identify 2 consecutive baseline days with breakthrough pain that could be assessed between 0700 and 1600 h.

2.2.2. OTFC dose titration

The OTFC dose titration phase followed the baseline data collection. Patients were given multiple OTFC units at a specific dose; only one unit dose was administered at a time. They were instructed to consume up to four separate OTFC units at 15 min intervals to treat a breakthrough pain. The goal of this phase was to gradually increase the size of the OTFC unit dose until the target breakthrough pain could be adequately treated using only a single OTFC unit.

Each day, up to two episodes of breakthrough pain between 0700 and 1600 h could be selected for OTFC treatment. The usual rescue drug was used to treat all other breakthrough pains on these study days. If two breakthrough pains were treated with the OTFC during a single day, a minimum of 2 h was required between the end of treatment for the first and the start of the second.

Once a pain was selected for OTFC treatment, the patient recorded pain data, then consumed an entire OTFC unit, if possible during a period of 15–20 min. To ensure that the drug was tolerated and that the decision to consume another unit was consistent with the protocol, patients were initially required to call the study nurse prior to taking the second or third OTFC unit.

All patients who entered the dose titration phase were randomly assigned to begin treatment with either a 200 or a 400 μg OTFC unit. All units were identical in appearance and both the patient and the investigator were blind to this starting dose. With the option to consume up to four units to treat a breakthrough pain episode, the full starting dose to treat a breakthrough pain could be as high as 800 μg for those randomized to receive the 200 μg unit and 1600 μg for those randomly assigned to receive the 400 μg unit.

The size of the OTFC unit dose could be increased or decreased on successive days. The available OTFC units contained 200, 400, 600, 800, 1200, or 1600 μg of fentanyl citrate. Each increase or decrease consisted of a change to the next step in this sequence of doses. For example, titration for a patient who received the 400 μg OTFC unit would consist of an increase to the 600 μg OTFC unit or a decrease to the 200 μg OTFC unit. When this new unit was used to treat a breakthrough pain, as many as four could be consumed at 15 min intervals, if needed.

The decision to titrate or maintain the dose for another day was made following a daily telephone assessment that evaluated response to the OTFC, including the number of units consumed and a global evaluation of analgesia and side effects. Simple guidelines were developed to encourage consistency in the investigators' judgments concerning dose titration. For example, investigators were encouraged to decrease the size of the OTFC unit if the patient consumed a single unit and experienced unacceptable side effects. Conversely, investigators were encouraged to consider a dose increase if no unacceptable side effects occurred and two or more units were required to provide adequate pain relief for an episode of breakthrough pain. All potential dose changes were discussed with the patient and a request for a change in dose was communicated to the pharmacist only if the patient agreed. New OTFC units were provided each time a decision to change the dose was made.

In contrast to the decision to reduce the dose, which was promptly implemented by the study pharmacist, the request to increase the dose was ignored one-third of the time to create additional uncertainty concerning the actual dose of OTFC. When the study pharmacist received a request to increase the dose, a separate randomization table was consulted that assigned each request into an 'increase dose' or 'ignore request' category. If the request for a dose increase was ignored, the following request was always fulfilled. Combined with the double-blind, random assignment to a starting dose, this second randomization and blinding procedure reduced the likelihood that the patient or investigator would know either the size of the dose or whether it represented a true increase over the prior dose.

The titration process continued until a dose of OTFC was found that provided adequate relief of the target pain on 2 consecutive days without the need to take more than one unit. On each of these days, one or two breakthrough pains could be treated with the OTFC. Patients who could not attain adequate relief of the breakthrough pain with a single 1600 μg dose, the highest strength available, and those who could not be adequately titrated during a maximum of 20 days, were removed from the study.

2.3. Outcome measures

All patients completed a questionnaire that provided detailed information about their persistent pain and breakthrough pains, and both disease-related and demographic information. On each day of the study, patients completed a daily diary that recorded global information about the persistent and breakthrough pain, pain treatments, and changes in medical condition. This information was used to ensure that the underlying pain syndrome remained stable during the study. On the evenings of the 2 baseline days and each OTFC treatment day, patients also recorded a global performance evaluation of the rescue drugs used during the day. These global performance scales ranged from 0 (poor) through 4 (excellent).

The primary outcome data comprised pain scores collected during treatment of one or two episodes of breakthrough pain during both baseline days and the 2 days following successful titration of the OTFC dose. Data collection was similar for all these episodes of breakthrough pain. Immediately before drug administration, patients recorded pain intensity in a study diary using an 11-point numerical scale (0, no pain; 10, pain as bad as you can imagine). Measurements of pain intensity and pain relief were recorded at approximately 15, 30 and 60 min after starting treatment. Breakthrough pains that required more than one OTFC unit were assessed at only 15 min after starting the dose. Pain was again evaluated on the 11-point numerical scale and pain relief was assessed using a four-point categorical scale (0, 'none'; 4, 'complete'). A global impression of the drug's performance, which used a rating from 0 (poor) through 4 (excellent), was recorded once daily. Based on the actual times of assessment recorded by the patients, the 15 min evaluation actually represents an interval of 10–20 min from the start of study drug consumption, the 30 min evaluation represents an interval of 25–35 min, and the 60 min evaluation represents an interval of 50–70 min.

Adverse events were elicited by the study nurse at the time of each patient contact. On the baseline days and the days that the OTFC was assessed, the study nurse inquired specifically about the occurrence of adverse effects related to the drug used to treat the breakthrough pain.

2.4. Data analysis

The scores on the instruments used to acquire pain intensity, pain relief and global performance data were averaged for each patient during each phase of the study. For example, the 15 min pain relief associated with the usual rescue dose during the baseline period was evaluated by averaging the 15 min pain relief scores for all the breakthrough pain episodes assessed during the baseline period (minimum of one per day for 2 days and maximum of two per day for 2 days). This overall pain relief score from each patient was then averaged across patients to yield a pain relief summary score for each phase of the study.

To evaluate pain intensity, pain intensity differences (PID) and the change in pain relief were calculated similarly. For example, the 0–15 min PID was calculated by subtracting the 15 min pain intensity score following consumption of the drug from the pain intensity score immediately prior to drug consumption for each episode of breakthrough pain. These PIDs were averaged within each patient for each study phase, then averaged again across patients. The 0–15 min PID was available for all assessed episodes of breakthrough pain; the 15–30 min PID and the 30–60 min PID were available only for those breakthrough pains evaluated during the 2 days of the baseline period and the 2 days following successful OTFC titration.

Outcome variables collected once daily, such as global performance of rescue drug, were also averaged for each patient within the same phase of the study. Averages of these scores across patients again yielded summary scores for the various phases of the study.

Continuous demographic data, pain severity at screening, log transformed medication level data, outcome data (pain intensity, PID, pain relief, global rating), number of titration increases, number of breakthrough pain episodes per day, and final OTFC dose level were analyzed using two-way analysis of variance, with terms for treatment group, site, and treatment group by site. A separate analysis was done for each phase that included the measurements performed in each phase. The objective was to compare the treatment groups.

Categorical data (gender, race, pain pathophysiology and pain syndrome, completion status) were analyzed with the Cochran Mantel Haenszel General Association Test. The comparisons of treatment groups were performed after stratifying on site. When comparing the two phases for outcome data, and when comparing the first to last OTFC doses, a paired t-test (pairing within patient) was used. When comparing the first dose outcome measures across patients, a one way ANOVA was used, with a term for treatment group. Relationship of final dose to type of pain was analyzed with a one-way ANOVA, with a term for type of pain, and the relationship of completion status to type of pain was analyzed using Fisher's Exact Test.

Finally, the association between OTFC dose and opioid effects was analyzed with a linear regression. For all analyses, a (two-sided) P-value < 0.05 was considered statistically significant.

3. Results

Sixty-seven patients who met the eligibility criteria were screened into the study. Two patients did not successfully complete the stabilization phase and never received OTFC. Two other patients began the OTFC titration phase but then experienced a change in pain and opioid requirement, and

were temporarily removed from the study. These two patients were later re-randomized in the study following improvement in their pain syndromes and stabilization. Thus, 65 patients were randomized to the different starting doses of OTFC and provided outcome data for analysis.

3.1. Patient characteristics

The characteristics of the 65 patients are described in Table 1. The mean (±SD) age was 53 ± 12 years. More than half (57%) of the patients were women and 82% were Caucasian. Fifty-five percent had cancers of the breast, colon, head or neck, or lung.

Table 1
Demographic, tumor-related, and pain-related information ($n = 65$)

	Mean ± SD (range)
Age (years)	53 ± 12 (26–74)
Height (cm)	168 ± 11 (150–196)
Weight (kg)	70 ± 21 (27–137)
Sex	*No. (%)*
Male	28 (43)
Female	37 (57)
Race	*No. (%)*
White	53 (82)
Black	5 (8)
Hispanic	7 (1)
Pain etiology (persist)[a]	
Tumor	51 (78)
Treatment	9 (14)
Other	5 (8)
Pain etiology (BT)[b]	
Tumor	51 (78)
Treatment	9 (14)
Other	5 (8)
Pain pathophy (persist)[c]	
Somatic	29 (45)
Visceral	14 (22)
Neuro	22 (34)
Pain pathophy (BT)[d]	
Somatic	28 (43)
Visceral	15 (23)
Neuro	22 (34)
Tumor type	
Breast	17 (26)
Lung	7 (11)
Colon	6 (9)
Head/neck	6 (9)
Other	29 (45)[e]

[a]Pain etiology (related directly to tumor, treatment, or other factors) of the persistent pain.
[b]Pain etiology (related directly to tumor, treatment, or other factors) of the target breakthrough pain.
[c]Inferred pathophysiology of the persistent pain (neuro = neuropathic).
[d]Inferred pathophysiology of the persistent pain (neuro = neuropathic).
[e]Other diagnoses: kidney-3, non-Hodgkins lymphoma-3, sarcoma-3, uterine-3, unknown primary-3, esophageal-2, pancreas-2, melanoma-2, Bartholin's gland carcinoma-1, Hodgkin's lymphoma-1, testicular-1, plasma cell dyscrasia-1, neuroepithelioma-1, liver-1, ovarian-1, prostate-1.

Three-quarters of the patients had persistent pain that could be ascribed to a direct effect of the tumor. In almost all cases, the target breakthrough pain was an acute exacerbation of the persistent pain. At screening, the mean (±SD) severity of the persistent pain (pain on average during the day) was 4.6 ± 2.5 on the 0–10 numeric scale, and the range was 0 to 10. There were no significant differences among treatment sites or between patients randomized to the 200 versus 400 μg OTFC dose on any of these variables, with the exception of pain intensity at screening; this pain rating varied across study sites ($P = 0.004$), but the comparisons between treatment groups were consistent at each site, as indicated by a non-significant treatment-by-center interaction ($P = 0.34$).

Most patients (92%) received controlled-release oral morphine as the opioid administered on a fixed schedule. The rescue opioid varied among short-acting morphine (52%), oxycodone (22%), hydromorphone (12%), hydrocodone (9%), and codeine (5%).

3.2. Baseline period

During the baseline period (that is, after criteria for stable dosing had been met), patients evaluated their regular rescue drug for 2 consecutive days, rating pain and other outcomes for up to two episodes per day and providing a global performance rating for each day. Patients subsequently randomized to the 200 μg OTFC starting dose did not vary from those who received the 400 μg dose in the number of breakthrough pain episodes during the baseline period.

For the purposes of comparison, the doses of all opioids were converted to morphine equivalent milligrams using standard relative potency estimates (Jacox et al., 1994). During the baseline period, the mean (±SD) daily dose of the scheduled opioid was 208 ± 177 mg and the mean (±SD) size of the usual rescue dose was 26 ± 22 mg (Table 2). The mean (±SD) ratio of the rescue dose:total daily dose of the scheduled drug was 0.15 ± 0.09, and the geometric mean was 0.12. The ratio ranged from 0.04 to 0.50; 25 patients (38%) had a ratio less than 0.10 and 15 patients (23%) had a ratio greater than 0.20. Thus, the ratio of rescue dose:total daily dose had a broad distribution that averaged 10–15%. Although there were significant differences in these doses across study sites, there was no treatment-by-center interaction and the comparisons across treatments at the various sites were, therefore, consistent.

Immediately prior to the rescue dose, the mean pain intensity score was approximately 6 on the 0–10 numeric scale. After 60 min, the pain intensity averaged 2.5. Between time 0 and 15 min, the pain intensity lessened by 32% of the total decline in pain; similar reductions in pain intensity occurred during each of the subsequent 15 min periods.

Mean pain relief scores at 15 and 30 min after the rescue

Table 2

Opioid consumption during the baseline period, following opioid stabilization in patients randomized to the 200 μg OTFC starting dose ($n = 32$) and the 400 μg OTFC starting dose ($n = 33$), and the total group ($n = 65$)

	200 μg	400 μg	Total
	No. (%)	No. (%)	No. (%)
Scheduled opioid[a]			
Morphine, long-acting	30 (94)	30 (91)	60 (92)
Hydromorphone	0 (0)	2 (6)	2 (3)
Oxycodone	2 (6)	0 (0)	2 (3)
Methadone	0 (0)	1 (3)	1 (2)
Rescue opioid			
Morphine, short-acting	19 (59)	15 (45)	34 (52)
Oxycodone	6 (19)	8 (24)	14 (22)
Hydromorphone	3 (9)	5 (15)	8 (12)
Hydrocodone	2 (6)	4 (12)6 (9)	6 (9)
Codeine	2 (6)	1 (3)	3 (5)
Opioid dose (mg)[a]	222 ± 173 (60–800)[b*]	195 ± 182 (60–800)[b]	208 ± 177 (60–800)[b]
Rescue dose (mg)	31 ± 27 (5–100)[b*]	21 ± 14 (5–60)[b]	26 ± 22 (5–100)[b]
Ratio of doses[c]	0.16 ± 0.10 (0.04–0.50)[b*]	0.14 ± 0.08 (0.04–0.33)[b]	0.15 ± 0.09 (0.04–0.50)[b]

[a]Total daily dose administered on a fixed schedule.
[b]All opioid doses converted to mg equivalent to morphine using standard relative potencies.
[c]Ratio of rescue dose: fixed schedule dose.
*Data are the mean ± SD (range).

dose were between 1 and 2 on the 0–4 verbal rating scale, which correspond to the descriptors 'slight' to 'moderate' pain relief. At 60 min, the pain relief improved to a mean of 2.5, which corresponds to the range 'moderate' to 'lots' of pain relief. The global performance of the usual rescue drug during the baseline period was 2.0 on the 0–4 verbal rating scale.

There were no significant differences between patients randomized to the 200 μg versus 400 μg starting doses in any of these outcome variables. Again, there were significant differences across study sites, but the treatment-by-center interactions were non-significant.

3.3. OTFC titration phase

Thirty-two patients were randomly assigned to receive the 200 μg OTFC starting dose. Twenty-five (78%) were successfully titrated until a single OTFC unit could adequately treat the breakthrough pain; 5 (16%) withdrew due to adverse events (see below), 1 (3%) withdrew for some other reason, and 1 (3%) could not be successfully treated even after titration to the 1600 μg OTFC unit size. Thirty-three patients were randomly assigned to receive the 400 μg OTFC starting dose. Twenty-three (70%) successfully completed the OTFC titration phase; 3 (9%) withdrew due to adverse events (see below), 3 (9%) withdrew for some other reason, and 4 (12%) could not be successfully treated at the 1600 μg OTFC unit size. There was no significant difference in the completion rate between randomly assigned groups. The category, 'withdrawal for other reasons,' included patients who left the study due to the cessation of breakthrough pain, chemotherapy, change in the fixed schedule drug, and refusal related to incomplete pain relief.

3.3.1. Dose response

Differences in the responses to the lower initial dose and higher last dose, or to the 200 and 400 μg starting dose, would indicate a dose response relationship and suggest the adequacy of the blinding procedures and the sensitivity of the methodology. An analysis of pain scores following the first and last doses of OTFC in all patients who underwent dose escalation demonstrated that the higher dose produced a significantly greater mean pain intensity difference ($P < 0.002$) and pain relief ($P < 0.0001$) at the 15 min assessment than the lower dose, as well as a better global rating ($P < 0.0001$).

A dose response was similarly supported by the finding that successfully treated patients who were randomized to the 200 μg dose required more dose increases than those randomized to the 400 μg dose (mean [±SD] of 1.56 ± 1.69 for the 200 μg dose versus 0.70 ± 0.88 for the 400 μg dose, $P = 0.051$). During the titration process, no patient required a dose decrement.

Finally, dose response was suggested by the patients' reaction to the blinding procedures for dose escalation. According to the randomization schedule, one-third of orders to increase the dose were ignored. Eleven of the 48 successfully titrated patients had orders for dose escalation ignored a total of 15 times. Of these 15 times, only three reported that the same dose was successful on the subsequent trial and 12 (80%) required further dose escalation to find an effective dose.

In contrast to the latter findings, analysis of pain scores

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Opioid consumption during the baseline period, following opioid stabilization in patients randomized to the 200 μg OTFC starting dose ($n = 32$) and the 400 μg OTFC starting dose ($n = 33$), and the total group ($n = 65$)

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There were no significant differences between patients randomized to the 200 μg versus 400 μg starting doses in any of these outcome variables. Again, there were significant differences across study sites, but the treatment-by-center interactions were non-significant.

3.3. OTFC titration phase

Thirty-two patients were randomly assigned to receive the 200 μg OTFC starting dose. Twenty-five (78%) were successfully titrated until a single OTFC unit could adequately treat the breakthrough pain; 5 (16%) withdrew due to adverse events (see below), 1 (3%) withdrew for some other reason, and 1 (3%) could not be successfully treated even after titration to the 1600 μg OTFC unit size. Thirty-three patients were randomly assigned to receive the 400 μg OTFC starting dose. Twenty-three (70%) successfully completed the OTFC titration phase; 3 (9%) withdrew due to adverse events (see below), 3 (9%) withdrew for some other reason, and 4 (12%) could not be successfully treated at the 1600 μg OTFC unit size. There was no significant difference in the completion rate between randomly assigned groups. The category, 'withdrawal for other reasons,' included patients who left the study due to the cessation of breakthrough pain, chemotherapy, change in the fixed schedule drug, and refusal related to incomplete pain relief.

3.3.1. Dose response

Differences in the responses to the lower initial dose and higher last dose, or to the 200 and 400 μg starting dose, would indicate a dose response relationship and suggest the adequacy of the blinding procedures and the sensitivity of the methodology. An analysis of pain scores following the first and last doses of OTFC in all patients who underwent dose escalation demonstrated that the higher dose produced a significantly greater mean pain intensity difference ($P < 0.002$) and pain relief ($P < 0.0001$) at the 15 min assessment than the lower dose, as well as a better global rating ($P < 0.0001$).

A dose response was similarly supported by the finding that successfully treated patients who were randomized to the 200 μg dose required more dose increases than those randomized to the 400 μg dose (mean [±SD] of 1.56 ± 1.69 for the 200 μg dose versus 0.70 ± 0.88 for the 400 μg dose, $P = 0.051$). During the titration process, no patient required a dose decrement.

Finally, dose response was suggested by the patients' reaction to the blinding procedures for dose escalation. According to the randomization schedule, one-third of orders to increase the dose were ignored. Eleven of the 48 successfully titrated patients had orders for dose escalation ignored a total of 15 times. Of these 15 times, only three reported that the same dose was successful on the subsequent trial and 12 (80%) required further dose escalation to find an effective dose.

In contrast to the latter findings, analysis of pain scores

following the first dose failed to reveal any significant differences between the 200 and the 400 μg dose. Although this outcome does not support a dose response relationship, it may be explained by the large number of patients who attained satisfactory analgesia after the lower starting dose. Approximately one-third of the patients who received the 200 μg dose reported that this dose was satisfactory. It is likely that many of the patients who received 400 μg would have responded to a lower dose and could not demonstrate much additional analgesia from that part of the dose in excess of 200 μg.

3.3.2. Drug exposure and other analgesic outcomes

Altogether, the 65 patients consumed 913 OTFC units to treat 489 breakthrough pains. As noted previously, OTFC unit dose sizes varied between 200 and 1600 μg, but patients could use up to four units to treat an episode of breakthrough pain. Twenty-six patients (40%) used only 200 or 400 μg doses to treat all episodes, and nine patients (15%) used doses of 3200–6400 μg to treat at least one episode. Similarly, 132 episodes (31%) were treated with a total dose of 200 or 400 μg, and 58 episodes (12%) were treated with a total dose of 3200–6400 μg.

The mean (±SD) dose of OTFC following successful titration was 640 ± 374 μg for those patients randomized to the 200 μg starting dose and 548 ± 202 μg for those who received the 400 μg starting dose. This difference was not significant ($P = 0.13$). Neither the final dose nor the likelihood of a successful titration was influenced by any characteristic of the patient, including type of pain. Most notably, a neuropathic mechanism did not reduce the likelihood of a favorable response to the OTFC.

In contrast to the usual rescue drug, there was no relationship between the successful dose of OTFC and the scheduled dose of opioid. The 200 or 400 μg dose was effective for more than half (54%) of the successful patients, irrespective of the total daily dose of the scheduled drug. Those who could not be successfully titrated despite escalation to the 1600 μg OTFC dose did not have a scheduled opioid dose higher than the successful patients; two of these unsuccessful patients received total daily doses (morphine 60 and 120 μg, respectively) that were substantially below the mean consumption, and only one patient received a dose that was >1 standard deviation above this mean dose.

The 48 patients who were successfully titrated assessed the response to a single OTFC unit during treatment of up to two breakthrough pains per day for each of 2 days, and provided a global performance rating for each day. Like the assessment prior to the usual rescue dose, the mean pain intensity immediately before the OTFC dose was approximately 6 on the 0–10 numeric scale. After 60 min, the pain intensity averaged 1.5. The reduction in pain intensity during the 0–15 min time period was 56% of the total pain intensity decline.

Mean pain relief scores at 15 and 30 min after the OTFC dose were 2.1 and 2.5, respectively, where 2 corresponds to the descriptor 'moderate' and 3 corresponds to the descriptor 'lots' of pain relief. At 60 min, the pain relief increased to a mean of 3.1. The global performance of the OTFC during the 2 successful treatment days was 2.9 on the 0–4 verbal rating scale.

With the exception of a single pain intensity difference recorded at the 60 min time point, there were no significant differences between patients randomized to the 200 versus 400 μg starting doses in any of these outcome variables. Although there were significant differences across study sites for some of the variables, in no case was the treatment-by-center interaction significant.

3.3.3. Time-action characteristics of usual rescue drug versus OTFC

A comparison of the time-action relationships of the usual rescue dose and the OTFC in successfully titrated patients ($n = 48$) also demonstrated a more rapid onset of analgesia following OTFC treatment (Fig. 1). In this subgroup, the decline in pain intensity during the initial 15 min period was 56% of the total pain reduction following OTFC and 32% of the total following the usual rescue dose ($P < 0.0001$). The amount of pain relief during this initial period was 65% of total pain relief for OTFC and 46% of total pain relief for the usual rescue dose ($P < 0.0001$).

3.3.4. Adverse events

During the OTFC titration phase, ten patients withdrew from the study due to adverse event. Two patients temporarily withdrew due to increasing intensity of the persistent pain, but were allowed to enroll a second time after their pain stabilized. Two patients withdrew due to events, i.e. an episode of dizziness, hallucinations, and body numbness, and an episode of dry mouth, headache, dizziness, and somnolence, judged by the investigators involved as 'probably' related to the OTFC, and two other patients withdrew due to events in an episode of somnolence associated with unrelieved pain and an episode of nausea and vomiting is judged to be 'possibly' related. The three other adverse events preceding withdrawal from the study were serious medical complications related to the underlying disease and unrelated to the OTFC; all resulted in hospitalization and one led to a patient death.

There were four other serious adverse events during the study, each of which resulted in hospitalization but did not require withdrawal from the study. One of these events, an episode of severe nausea, constipation, and dehydration, was considered to be 'possibly' related to the OTFC by the investigator involved. The others represented unrelated complications attributable to the underlying disease or associated comorbidity.

The side effects associated with the OTFC were typical opioid-related events. On the days that any OTFC was taken, side effects that occurred with a frequency of ≥5% and were considered by the investigator to be 'possibly,' 'probably,' or 'almost certainly' associated with the study

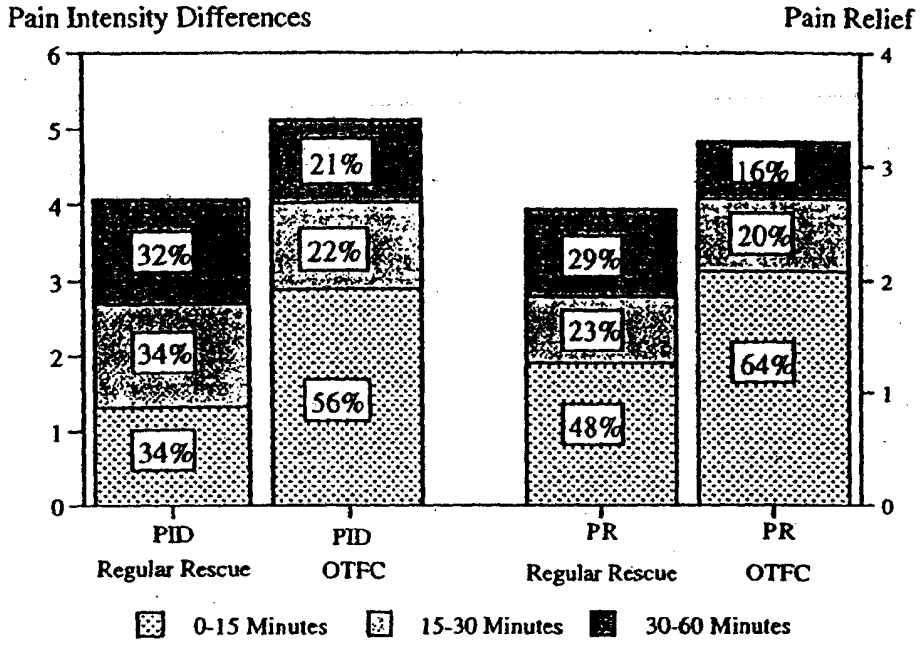

Fig. 1. Change over time in mean pain intensity and mean pain relief produced by OTFC and the usual rescue dose in all patients who were successfully titrated to an effective OTFC dose and assessed their usual rescue drug during the baseline period ($n = 48$).

drug comprised somnolence (28%), dizziness (14%), nausea (10%) and headache (5%). During the last 2 days of OTFC administration, when the OTFC dose had been appropriately titrated, the side effects that occurred with a frequency of ≥5% and were considered to be at least 'possibly' related to the study drug again included somnolence (15%), dizziness (6%), and nausea (5%).

To assess the dose response for these non-analgesic effects, an 'opioid effect score' was calculated as the total number of adverse events perceived by the investigators as 'possibly,' 'probably,' or 'almost certainly' associated with the study drug and occurring on the days that OTFC was consumed. Numerous potential adverse effects were included in the score: asthenia, confusion, constipation, dizziness, dry mouth, dyspepsia, hypotension, nausea, nausea and vomiting, somnolence, sweating, syncope, urinary retention, vasodilation, vertigo, and vomiting. The possible range was 0 to 16 symptoms. The mean (±SD) score of those patients whose highest OTFC unit dose was 200 μg was 0.25 ± 0.62. The 400, 600, 800 and 1600 μg unit doses were associated with scores of 0.48 ± 0.98, 0.93 ± 0.92, 1.00 ± 1.53, and 1.25 ± 1.28, respectively. Despite a mean score of 0 for the three patients who consumed the 1200 μg unit dose, there was a trend towards statistical significance in the association between dose and these non-analgesic opioid effects ($P = 0.06$), further indicating a dose response relationship.

4. Discussion

Breakthrough pain is a highly prevalent clinical phenomenon that undermines the overall benefit of opioid therapy for chronic cancer pain (Mercadante et al., 1992; Bruera et al., 1995). Clinicians who manage cancer pain recognize the importance of specific interventions for the management of breakthrough pain, and commonly implement recommended guidelines for the use of a rescue drug in combination with scheduled opioid therapy (Jacox et al., 1994; Levy, 1996). These recommendations, which are based entirely on anecdotal experience, favor the selection of a short-acting opioid at a dose proportionate to the total daily dose.

Given the widespread use of rescue dosing, the lack of systematic clinical investigation of breakthrough pain and its therapies is remarkable. There have been no drugs or drug formulations developed specifically for breakthrough pain and, prior to this study, there have been no controlled clinical trials that evaluate the pharmacology of those drugs and formulations conventionally used for this indication.

The difficulties inherent in studying breakthrough pain probably contribute to the lack of data. Breakthrough pain is extremely heterogeneous (Portenoy and Hagen, 1990), and may vary in frequency, onset and duration, severity, quality, etiology and pathophysiology, and impact. It is only sometimes predictable and can vary from episode to episode in the same patient. The methodological challenge in studying a highly variable, subjective phenomenon that may or may not occur during any planned assessment period is evident.

OTFC is the first drug therapy undergoing investigation as a treatment for breakthrough pain, and the first to be evaluated in controlled clinical trials (Farrar et al., 1998).

The present study evaluated the safety and efficacy of ascending doses of OTFC using a novel controlled dose titration methodology that applied blinding and randomization procedures to the evaluation of recurrent pains in the home environment. The results are, therefore, informative in terms of both the formulation itself and the methodological considerations that must be addressed in future therapeutic trials that target breakthrough pain.

OTFC is a novel formulation of the highly potent and lipophilic synthetic opioid, fentanyl citrate. In the OTFC formulation, fentanyl is incorporated in a sweetened matrix, which is dissolved in the mouth. Part of the dose is absorbed transmucosally and part is swallowed, yielding pharmacokinetics unique to the formulation (Stanley et al., 1989; Streisand et al., 1991). Based on these kinetics and an anecdotal clinical experience (Fine et al., 1991), it has been postulated that OTFC may offer characteristics, such as a rapid onset and short duration, that favors its use as an intervention for breakthrough pain.

The present study used two separate blinding and randomization procedures to ensure that neither the patient nor the investigator knew the actual dose administered during the study period. Dose response relationships were found for both analgesic outcomes and the occurrence of non-analgesic effects, suggesting that the methodology was sensitive to opioid effects. The results demonstrated that 74% of patients were able to identify a safe and effective dose of OTFC, which could adequately treat a target breakthrough pain with a single unit. In contrast to expectations, there was no relationship between the total daily dose of the scheduled opioid regimen and the dose of OTFC required to effectively manage the breakthrough pain. The time-action relationship of the OTFC also differed from the usual oral rescue drug in providing a significantly greater analgesic effect during the initial 15 min after the dose. Adverse effects of the OTFC were generally tolerable and typically opioid-related, specifically somnolence, nausea, and dizziness.

This study was not designed to validly compare the analgesic efficacy of OTFC with the usual rescue drug, and additional randomized trials will be necessary to confirm the observation that OTFC yielded more rapid and more complete analgesia, and better patient-rated global performance, than the usual rescue administered during an optimally titrated opioid regimen. Based on the results of this study, it may be hypothesized that OTFC produces better outcomes in at least some patients and, further, that it may be the more rapid onset of effect produced by transmucosal drug absorption that is the major factor that determines this better outcome.

Current guidelines for opioid therapy recommend that the size of an oral or parenteral rescue dose should be calculated as a proportion of the dose administered on a scheduled basis (Portenoy and Hagen, 1990; American Pain Society, 1992; Jacox et al., 1994; Levy, 1996). This guideline, which is based on anecdotal observations, led to the expectation of a relationship between the OTFC dose and the total daily opioid dose. For unknown reasons, this relationship was not found. Additional studies will be needed to confirm this finding and explore potential explanations. For the present, recommendations to begin OTFC dosing with the smallest dosage size (200 μg) and then titrate, are prudent. Since the dose required to treat a breakthrough pain may be related to the duration of the pain, future studies should better define the temporal relations of the target breakthrough as a possible covariate that may explain some aspect of the dose response relationships.

This study illustrates the potential for investigation of breakthrough pain using controlled trials methodology. The feasibility of blinding and randomization procedures in studies of recurrent pains in the home environment has been well demonstrated in headache trials (Schachtel et al., 1991). The present study confirms that this approach is also possible in medically-ill cancer patients with chronic pain and intermittent breakthrough pain. The use of an opioid stabilization period presumably yielded more reliable baseline data and the use of graded OTFC starting doses provided a means to evaluate the sensitivity of the methodology to drug effects (Max and Portenoy, 1993). The assessment of multiple pains yielded more experience with the study drug and more outcome data, and the evaluation of pain characteristics as potential covariates allowed secondary analyses that could have yielded clinically important information.

Some limitations in the design are also apparent, however, and should be addressed in future studies. As noted previously, the study was not intended to validly compare analgesic efficacy of OTFC and the usual rescue dose, and this comparison must be considered tentative given the potential for an order effect and differential placebo effects in the two treatments. However, the highly significant differences between the regular rescue and OTFC are intriguing and should be investigated further. Although the assessment of multiple breakthrough pains presumably increased the stability of the data, it could also introduce carryover effects, which could be pharmacokinetic or conditioned. Systematic evaluation of this possibility may also be warranted in future studies. Finally, the use of the usual rescue drug during the OTFC dose titration period to treat pains that could not be treated with the OTFC, could have potentially altered the expectations about the OTFC and introduced a systematic bias in the responses. Again, future studies may wish to consider a separate drug for the rescue doses that are not investigated.

These limitations notwithstanding, the present study represents an important step in applying analgesic trials methodology to the important phenomenon of breakthrough pain. The data suggest that OTFC can be a safe and effective drug for this problem. Further studies into its dose response relationships, pharmacokinetic-pharmacodynamic relationships, and comparative benefits and risks in diverse patients and varied types of breakthrough pain are warranted.

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Dose-Titration, Multicenter Study of Oral Transmucosal Fentanyl Citrate for the Treatment of Breakthrough Pain in Cancer Patients Using Transdermal Fentanyl for Persistent Pain

By Joan M. Christie, Mary Simmonds, Richard Patt, Paul Coluzzi, Michael A. Busch, Earl Nordbrock, and Russell K. Portenoy

Purpose: **Supplemental, "as-needed," administration of an opioid is a common approach to the problem of breakthrough pain in cancer patients. Oral transmucosal fentanyl citrate (OTFC) is undergoing investigation as a new treatment for breakthrough pain. The primary purpose of the study was to demonstrate that a single-unit dose of OTFC can safely and effectively treat breakthrough pain. A secondary goal was to determine appropriate dosing guidelines.**

Patients and Methods: **This was a multicenter, randomized, double-blind, dose-titration study in 62 adult cancer patients using transdermal fentanyl for persistent pain. Consenting patients provided 2 days of baseline data to evaluate the performance of their usual breakthrough pain medication. Patients then randomly received 200 μg or 400 μg OTFC in double-blind fashion. (Patients were always assigned, rather than randomized, to 200 μg if 400 μg represented > 20% of around-the-clock medication.) Pain intensity (PI), pain relief (PR), and global satisfaction scores were recorded. OTFC was then titrated until the patient received adequate PR for each episode using one OTFC unit. Orders to titrate up were ignored one third of the time to improve the blind. Two days of baseline data were compared with 2 days of OTFC data after titration identified an effective dose of OTFC.**

Results: **Most patients (76%) found a safe and effective dose of OTFC. [redacted] In open-label comparisons, OTFC produced a faster onset of relief and a greater degree of PR than patients' usual breakthrough medication. Somnolence, nausea, and dizziness were the most common side effects associated with OTFC.**

Conclusion: **Most patients find a single OTFC dosage that adequately treats breakthrough pain. The optimal dose is found by titration and is not predicted by around-the-clock dose of opioids.**

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MOST PATIENTS WITH CANCER experience persistent pain and are treated with a fixed-schedule opioid regimen for their persistent pain.[1-4] Episodic acute pain commonly occurs in these patients.[5-11] This episodic pain is typically described as breakthrough pain. Breakthrough pain is highly prevalent, may have adverse consequences on the efficacy of analgesic therapy, and may have a negative impact on a patient's quality of life.[5-8]

Guidelines for cancer pain management recommend the use of an "as-needed" drug for the treatment of breakthrough pain.[9,10] This approach has been based on favorable anecdotal observations, and specific recommendations vary widely. However, the most common suggestions for the size of the breakthrough medication dose range from 5% to 15% of the total daily dose.[11-15]

Desirable attributes of a breakthrough pain medication include rapid onset, duration of effect as long as the typical duration of these pain episodes, no long-acting active metabolites, availability in a noninvasive formulation, and low cost. This is the first report of an opioid formulation that has been specifically investigated as a treatment for breakthrough pain.

Oral transmucosal fentanyl citrate (OTFC) is a fentanyl delivery system that imbeds the drug in a sweetened matrix on a handle. The matrix dissolves in the mouth and delivers part of the dose through the buccal and sublingual mucosa. The lipophilic nature of fentanyl facilitates absorption. The pharmacokinetic attributes of OTFC in normal volunteers are similar to attributes for a desirable breakthrough pain

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medication[16] and this drug is undergoing investigation as a potential therapy for this type of pain. These investigations have been designed to clarify the safety and efficacy of OTFC in treating breakthrough pain, to establish the best method of dosing, and to compare OTFC with other breakthrough pain medications.

The efficacy of specific treatments for breakthrough pain have not been previously studied. This controlled titration study was designed to evaluate systematically the safety and efficacy of ascending doses of OTFC in a blinded fashion. In the present study, patients who were using transdermal fentanyl to treat persistent pain were given OTFC for their breakthrough pain. The purpose was to demonstrate that a titration process can identify a dose of OTFC that can be delivered by a single-dosage unit to treat breakthrough pain safely and effectively. Random assignment to the starting dose of OTFC and random ignoring of orders to increase the dosage level were both done in a double-blind fashion to ensure that the patients and study staff were unaware of the actual dose administered as dose titration ensued. This allowed us to explore whether the optimal OTFC dose could have been predicted, for example, by the dose of transdermal fentanyl used to treat the persistent pain. A secondary objective was to compare the efficacy produced by OTFC with the efficacy produced by patients' usual breakthrough pain medications in an open-label manner.

PATIENTS AND METHODS

This was a randomized, double-blind, dose-titration study of 200 to 1,600 μg OTFC (Actiq; available in 200-, 400-, 600-, 800-, 1,200-, and 1,600-μg dosage units; Abbott Laboratories, North Chicago, IL) for the treatment of breakthrough pain in cancer patients using transdermal fentanyl. This multicenter study was conducted at 11 sites geographically dispersed throughout the United States. The protocol was approved by the investigational review boards (IRBs) for each study site and patients provided written informed consent.

Patients

From January 1995 until July 1996, 62 cancer patients who were using transdermal fentanyl (50 to 300 μg/h) for pain associated with their disease participated in the study. Eligible patients had stable pain, defined as persistent pain no more than moderate on average, tolerable opioid side effects, and the use of four or fewer doses of opioid medication for breakthrough pain daily. If patients had more than one type of breakthrough pain or had breakthrough pain in more than one location, they were asked to identify only one of the pains and consider it their "target" breakthrough pain. Study drug was used only to treat the patient's target breakthrough pain.

Methods

The study consisted of two phases: baseline and OTFC phase. In the baseline phase, patients' breakthrough pain and the performance of their usual breakthrough pain medication were assessed for 2 consecutive days. In the OTFC phase, patients were titrated to an effective dose of OTFC and the performance of this dose was evaluated. The data were used to examine the success of the titration process, the existence of dose-response relationships of OTFC, and the comparison of outcomes during 2 days of baseline treatment and 2 days of OTFC treatment once patients had titrated to an effective dose of OTFC.

The OTFC phase began immediately after completion of the baseline phase. Patients were randomly assigned to receive either 200 or 400 μg OTFC as a starting dose. The patient and the study personnel who interacted with the patient were not aware of the dose. To ensure safety, patients taking less than 100 μg/h transdermal fentanyl were always assigned to start with the 200 μg OTFC.

On each study day, as many as four OTFC units could be taken sequentially (one every 30 minutes) for up to two breakthrough pain episodes. If more than one unit was needed to treat a pain episode, the investigator could order titration of the dose to the next largest OTFC unit size. The dosage unit size could also be decreased at the discretion of the investigator. The goal of the dose titration phase was to identify the dose of OTFC for each patient that was adequate to treat one episode of breakthrough pain using a single unit. To enhance the blind further, orders to increase the dosage were randomly ignored one third of the time by an unblinded dispensing pharmacist, according to a randomization schedule. As a result, the patient and the investigator were not aware of the actual dosage delivered during the titration process.

Dose titration continued until the patient completed 2 consecutive successful days of treatment with OTFC. A day was considered successful when a patient achieved adequate relief of breakthrough pain using only one OTFC unit per episode and did not require a dose adjustment.

Study Variables

For each breakthrough pain studied, pain intensity (PI) scores were obtained before use of breakthrough pain medication (usual breakthrough medication during the baseline phase and OTFC during the OTFC phase). PI and pain relief (PR) were reported at 15, 30, and 60 minutes following treatment. If a second dose of OTFC was needed to manage the pain, outcome data were collected at 15 minutes only. At the end of each day, patients provided a global evaluation of the performance of usual breakthrough pain medication or OTFC. Side effects were also recorded.

Patients evaluated PI using a categorical rating scale that ranged from 0 (no pain) through 10 (pain as bad as you can imagine). Pain-intensity differences (PID) were obtained by calculating the change in PI at each time point compared with the 0-minute score. Patients rated PR using a five-point scale ranging from 0 (none) to 4 (complete). The global satisfaction scale, which evaluated the patients' overall satisfaction with the study medications, ranged from 0 (poor) through 4 (excellent).

Statistical Calculations

Before the OTFC studies, no reports of studies for breakthrough pain were found in the literature. Thus, no effect size was available for estimating sample size. Based on discussions with leading cancer pain experts, it was determined that approximately 60 patients should be enrolled to obtain meaningful experience with OTFC for managing breakthrough pain.

Within-patient averages (for each of baseline phase and titration phase) were computed and these averages were the data analyzed. Thus, for example, if a patient had four episodes on the 2 consecutive baseline days, the average of the four PIs at time zero was calculated for each patient. These within-patient phase averages were analyzed with the following statistical methods.

When comparing the randomized dose groups (200 μg *v* 400 μg starting dose), a two-way analysis of variance (ANOVA) with terms for

treatment group, site, and treatment by site was used when analyzing PI, PID, PR, number of titration increases, and successful OTFC dose level. Fisher's exact test was used to analyze completion status.

When comparing the two phases, a signed-rank test (pairing is within patient) was used to analyze global satisfaction. A three-way ANOVA with terms for site, subjects within site, phase, and site by phase was used to analyze PI, PID, and PR. Relationship of final dose to type of pain was analyzed with a one-way ANOVA with term for type of pain.

A two-sided P value $\leq .05$ was considered statistically significant.

RESULTS

Patient Characteristics

Approximately half of the patients were female (53%) and the median age was 59 years (range, 25 to 91). The most common diagnosis was lung cancer (26%), followed by breast cancer (11%) and prostate cancer (10%) (Table 1). Pain characteristics and syndromes were tabulated using a checklist. In nearly all cases, the patient's predominant persistent and target breakthrough pain had the same pathophysiology and syndrome, which suggests the patient's breakthrough pain was most likely an acute exacerbation of their persistent pain (Table 2). Sixteen percent of the persistent and breakthrough pain was neuropathic. Approximately 80% of target pain was related to direct tumor involvement, most involving lesions of somatic and visceral structures. Four patients had pain syndromes that were related to cancer therapy. One was secondary to a postradical neck dissection, two to radiotherapy, and one syndrome was due to postchemotherapy aseptic necrosis of bone.

Table 1. Demographic and Baseline Characteristics of Patients

Variable	Total (N = 62) No.	%
Sex		
Female	33	53
Male	29	47
Age, years		
Mean	59	
Range	25-91	
< 35	4	6
35-65	40	65
> 65	18	29
Race		
Asian	2	3
Hispanic	3	5
White	57	92
Cancer diagnosis		
Lung	16	26
Breast	7	11
Prostate	6	10
Pancreatic	5	8
Ovarian	5	8
Head/neck	3	5
Colon/rectal	3	5
Gastroesophageal	2	3
Leukemia	2	3
Unknown primary	2	3
Miscellaneous*	11	18

*Miscellaneous diagnosis (1 occurrence each) included appendix, basal cell carcinoma, brain, carcinoid tumor, giant cell tumor of sacrum, kidney, non-Hodgkin's lymphoma, melanoma, myelofibrosis, schwannoma, and uterine.

Table 2. Predominant Pain Pathophysiology and Syndrome for Persistent and Target Breakthrough Pain (N = 62)

Pain Characteristic	Persistent No.	%	Target Breakthrough No.	%
Pathophysiology				
Nociceptive—somatic	35	57	34	55
Nociceptive—visceral	17	27	18	29
Neuropathic	10	16	10	16
Syndrome				
Pain related to direct tumor involvement				
Due to somatic/visceral structure lesions	50	81	48	77
Neoplastic damage to bone and joints	26	42	24	39
Neoplastic damage to viscera	12	19	13	21
Neoplastic damage to soft tissues & miscellaneous syndromes	12	19	11	18
Due to nervous tissue lesions	5	8	6	10
Pain related to therapy	4	7	4	7
Unknown	0	0	1	2
Other	3	5	3	5

Baseline Phase

Table 3 lists the opioid medications patients were taking during the baseline phase of the study. All patients were using oral formulations of opioids to treat their breakthrough

Table 3. Summary of Pain Medications at Baseline

Variable	Total (N = 62) No.	%
Transdermal fentanyl dose, μg/h (mean ± SD)	103 ± 63	
Regular breakthrough medication dose, mg/episode* (mean ± SD)	21 ± 20	
Patients' breakthrough medications		
Oxycodone†	16	26
Morphine, short-acting†	15	24
Hydromorphone	11	18
Hydrocodone†	10	16
Propoxyphene†	6	10
Codeine†	2	3
Tramadol	1	2
None	1	2

*Morphine equivalent dose for each episode of breakthrough pain.
†In most cases, supplied as a combination product.
‡Either as tablet or oral solution.

Table 4. Summary of Patient Completion Status (N = 62)

Completion Status	ATC Dose 50-75 μg/h, Patients Assigned to Starting Dose: 200 μg (n = 33) No.	%	ATC Dose 100-300 μg/h, Patients Randomized to Starting Dose: 200 μg (n = 18) No.	%	400 μg (n = 11) No.	%	Total (N = 62) No.	%
Completed study successfully	26	79	13	72	8	73	47	76
Insufficient relief of pain with 1,600 μg OTFC	1	3	3	17	0	0	4	6
Withdrew from study								
OTFC-associated SE*	2	6	0	0	1	9	3	5
Non-OTFC-associated SE	1	3	1	6	1	9	3	5
Reason(s) other than SE†	3	9	1	6	1	9	5	8

NOTE. Fisher's exact test, $P = .49$ for determining whether completion status is different between the 200- and 400-μg randomized starting groups (OTFC-associated side effects and non-OTFC-associated side effects were combined for analysis).

Abbreviation: SE, side effects.

*SE included shortness of breath, chest pains, disorientation, unsteady gait, and weakness in 1 patient and dizziness and blurred vision in the other.

†Reasons included patient's unwillingness to comply with study procedures, inadequate PR, inability to consume OTFC, and travel.

pain. Approximately one fourth of patients (26%) were using oxycodone and one fourth (24%) were using short-acting morphine as the breakthrough pain medication. The remainder used a variety of other analgesics. The mean ± SD dose of transdermal fentanyl was 103 ± 63 μg/h. To summarize, the doses of breakthrough pain medication were converted to morphine equivalent milligrams using standard relative potency estimates.[10] The mean ± SD dose was equivalent to 21 ± 20 mg/episode.

Patients experienced about three episodes of breakthrough pain per day during the baseline phase. Mean PI decreased by approximately 50% over the 60-minute period following ingestion of the usual breakthrough pain medication. Immediately before the breakthrough medication dose, patients had mean PI scores of 6.0. By 60 minutes, mean PI scores had decreased to 2.8. The decrement in PI was approximately the same from 0 to 15 minutes, 15 to 30 minutes, and 30 to 60 minutes, respectively. PR showed a similar response over the hour. By 60 minutes, mean PR scores were about 2.3, which indicates "moderate" to "lots" of pain relief.

OTFC Phase

Thirty-three patients using transdermal fentanyl doses of less than 100 μg/h were assigned to start at 200 μg OTFC to ensure that their initial dose of OTFC did not exceed 20% of their around-the-clock medication. The other 29 patients were randomized, with 18 randomized to receive the 200-μg dose of OTFC and 11 randomized to start at the 400-μg dose of OTFC.

Seventy-six percent of all patients (47 of 62) who enrolled onto the study were successfully titrated to a unit dose of OTFC that effectively treated their breakthrough pain and completed the study. Only four patients (6%) were unable to control their breakthrough pain with the highest OTFC dose unit offered (1,600 μg). Eleven patients withdrew from the study; six of these withdrawals were due to a side effect. Only three patients were withdrawn due to side effects related to the study drug. There was no difference between the randomized treatment groups (200-μg *v* 400-μg starting dose) in the completion status ($P = .49$). Table 4 lists patients' completion status.

Patients who found a successful dose of OTFC were titrated to a mean dose of approximately 600 μg (Table 5). There was no statistically significant difference in final dose between the patients who began with the 200-μg and those who began with the 400-μg doses (677 μg *v* 825 μg, respectively; $P = .58$). Patients who were assigned to the 200-μg starting dose titrated to a mean dose of 469 μg. For all three groups combined (the two randomized groups and

Table 5. Final Dose of OTFC for Patients Who Found a Successful Dose

Final Dose (μg)	ATC Dose 50-75 μg/h, Patients Assigned to Starting Dose: 200 μg (n = 26) No.	%	ATC Dose 100-300 μg/h, Patients Randomized to Starting Dose: 200 μg (n = 13) No.	%	400 μg (n = 8) No.	%	Total (N = 47) No.	%
200	13	50	6	46	—		—*	
400	8	31	2	15	1	13	30	64
600	3	12	2	15	1	13	6	13
800	1	4	0	0	5	63	6	13
1,200	1	4	1	8	0	0	2	4
1,600	0	0	2	15	1	13	3	6
Modified† mean ± SD	469 ± 178		677 ± 466		825 ± 345		587 ± 335	

Abbreviation: ATC, around-the-clock.

*200-μg and 400-μg doses were combined as 400 μg.

†For the 200-μg group, 200 μg taken as 400 μg when computing mean, SD, and SEM, and for statistical analysis.

the assigned group), nearly two thirds (64%) of all successful patients found the 200-μg or 400-μg dose effective. Patients who found a successful dose of OTFC had a mean (± SD) dose increase of 1.19 ± 1.41 to reach their final dose and there was no statistically significant difference between the randomized starting groups (1.54 ± 1.94 *v* 1.88 ± 1.13 for the 200-μg and 400-μg doses, respectively, $P = .67$; 0.81 ± 1.06 for the assigned group). A dose increase occurred when an investigator ordered an increase and the randomization allowed the increase; orders to increase that were ignored were not counted as an increase.

Several exploratory analyses were performed to try to predict the successful OTFC dose. Figure 1 shows the final dose of OTFC in relation to the patients' transdermal fentanyl dose for patients who were successfully titrated. Although the slope is significant ($P = .002$), only 19% of the variability of the final OTFC dose was explained by the transdermal fentanyl dose level. Figure 2 shows a linear regression of the final dose of OTFC versus the usual breakthrough medication. The overall slope was significant ($P \leq .0001$). This indicates that, in successful patients, regular rescue dose was a moderate predictor (linear regression $R^2 = 44\%$) of the effective OTFC dose. In addition, there was no relationship between the dose of OTFC required to treat the breakthrough pain and the inferred pathophysiology of the pain (nociceptive *v* neuropathic) ($P = .54$).

The 47 patients who were successfully titrated assessed the response to a single OTFC unit during the treatment of up to two breakthrough pains per day for each of 2 days. Mean pain scores on successful days for the randomized and assigned groups are listed in Table 6. Starting dose generally did not influence the efficacy of OTFC once a successful dose was determined, with nonsignificant treatment *P* values

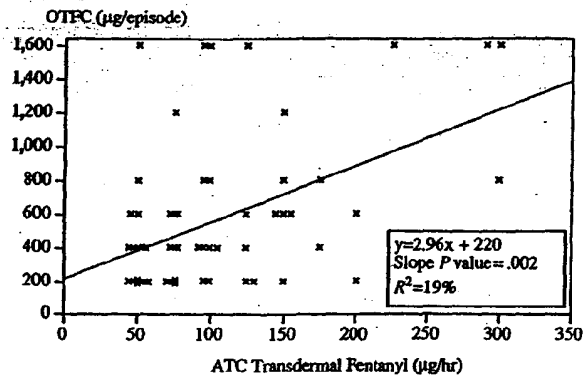

Fig 1. Final dose of OTFC in relation to transdermal fentanyl for all patients who found a successful dose in the range offered (N = 47); *P < .0001, 3-way ANOVA.

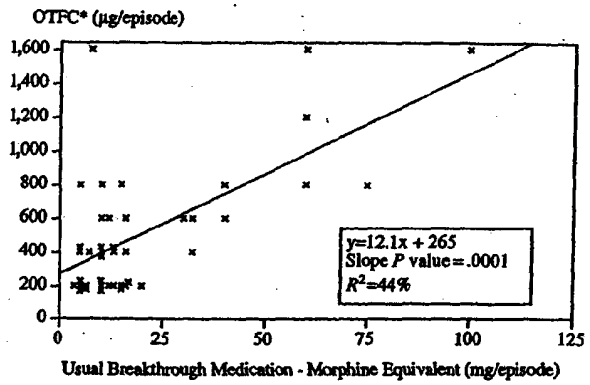

Fig 2. Final dose of OTFC in relation to usual breakthrough medication for patients who found a successful dose and were randomized to 200-μg or 400-μg starting dose (n = 21). *200- and 400-μg doses combined as 400 μg.

at every observation point for PI, PID, and PR, except for PR at 60 minutes.

Comparison of Usual Breakthrough Pain Medication and OTFC.

Pain scores following OTFC on successful days were compared with pain scores on baseline days following usual breakthrough medication. Although this comparison is not blinded, it does provide some indication of how effective OTFC was in this model. Scores at 0 minutes (immediately before the drug was taken) were not significantly different for the two. At 15, 30, and 60 minutes, OTFC produced markedly lower PI scores and higher PR scores than the usual breakthrough pain medication ($P \leq .0002$ for each analysis). At 30 minutes, the mean (± SD) difference between PI scores following usual breakthrough pain medication and OTFC was 1.6 ± 1.9. PID scores at 15, 30, and 60 minutes were also significantly better following OTFC ($P \leq .0001$). The 0- to 15-minute PID score for OTFC was over 2½ times larger than the score for usual breakthrough pain medication (2.35 *v* 0.91, $P = .0001$), consistent with a faster onset of OTFC (Fig 3). Similarly, OTFC produced a PR score at 15 minutes that was more than two times higher than the score produced with the usual breakthrough pain medication (1.90 *v* 0.82, $P = .0001$) (Fig 3). At 30 minutes, the mean (± SD) difference between scores following each treatment was 0.95 ± 1.2.

In addition, the global satisfaction ratings were significantly higher following OTFC compared with usual breakthrough pain medication (2.6 *v* 2.0, $P = .0001$).

Site interactions were evaluated for all of the study's main variables. When pain scores were evaluated for study-site interactions, there was a significant phase by site interaction (baseline phase *v* OTFC phase) for PID at 15 minutes and PR at 15 and 30 minutes. Subsequently, pairwise compari-

Table 6. Mean ± SD Measurements of OTFC on Successful Days in Patients Who Found a Successful Dose of OTFC (N = 47)

Variable (minutes)	ATC Dose 50-75 μg/h, Patients Assigned to Starting Dose	ATC Dose 100-300 μg/h, Patients Randomized to Starting Dose		Mean Difference Between Randomized 200-μg and 400-μg Groups	90% CI
	200 μg (n = 26)	200 μg (n = 13)	400 μg (n = 8)		
PI*					
0	6.4 ± 1.5	1.8 ± 1.6	6.8 ± 1.9	− 0.85	− 2.61-0.92
15	4.1 ± 2.1	3.9 ± 2.3	3.8 ± 2.2	0.13	− 1.75-2.02
30	2.4 ± 1.7	2.4 ± 1.7	3.1 ± 2.0	− 0.64	− 2.01-0.74
60	1.8 ± 1.6	1.8 ± 1.7	2.1 ± 1.8	− 0.34	− 1.73-1.06
PID					
15	2.3 ± 2.0	2.2 ± 1.9	2.7 ± 1.1	− 0.53	− 1.87-0.81
30	4.0 ± 2.1	3.5 ± 2.0	3.7 ± 1.1	− 0.20	− 1.55-1.15
60	4.5 ± 1.9	4.3 ± 1.9	4.6 ± 1.3	− 0.23	− 1.57-1.10
PR†					
15	1.8 ± 1.0	1.9 ± 1.3	2.1 ± 0.7	− 0.19	− 1.09-0.72
30	2.6 ± 1.0	2.5 ± 0.8	2.3 ± 0.7	0.24	− 0.36-0.83
60	2.9 ± 0.9	3.0 ± 0.8	2.8 ± 0.9	0.25	− 0.40-0.90

NOTE. When comparing randomized 200-μg versus randomized 400-μg starting doses, all treatment 2-way ANOVA *P* values, except PR at 60 minutes, were nonsignificant. At PR 60 minutes, $P = .04$. Only randomized groups were included in statistical analysis.

*PI scale: 0 = no pain through 10 = pain as bad as you can imagine.

†PR scale: 0 = none through 4 = complete.

son follow-up evaluations for these interactions were performed. The results indicated that the difference between the usual breakthrough medication and OTFC were different at a pooled site than at four of the unpooled sites. These differences were not deemed to bias the results and interpretation.

Side Effects

During OTFC titration, when patients could use multiple units of OTFC to treat an episode of breakthrough pain, doses up to 6,400 μg per episode was used safely. The side effects associated with OTFC were typical opioid-related effects. The most common side effects on days that any OTFC was taken and were considered possibly, probably, or almost certainly related to OTFC were somnolence (18%), nausea (11%), dizziness (10%), and vomiting (5%). During the final 2 days of the study, when OTFC had been appropriately titrated, side effects considered possibly, probably, or almost certainly related were somnolence (11%), nausea (10%), and dizziness (5%). During the 2-day baseline phase, when patients used their usual breakthrough pain medication, no side effect was experienced by more than 2% of patients. During the OTFC titration phase, six patients withdrew from the study due to adverse events. Four of the patients withdrew due to opioid side effects such as dizziness, nausea, vomiting, or weakness. One patient withdrew because of increasing persistent pain and another withdrew due to an exacerbation of anxiety.

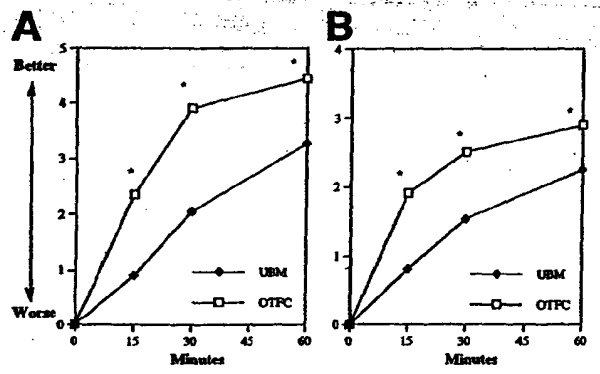

Fig 3. PID and PR scores (0 = no relief, 4 = complete) following usual breakthrough pain medication (UBM) and OTFC for patients who found a successful dose of OTFC (N = 47); *$P \leq .0001$.

Four patients experienced adverse events that necessitated hospitalization. None of these patients required withdrawal from the study. Three of these adverse events were unrelated to OTFC and were caused by the patients' underlying disease. One patient was hospitalized for abdominal pain, which the investigator could not rule out as being possibly related to OTFC.

DISCUSSION

Breakthrough pain in cancer patients is poorly understood. The scant available data suggest that the prevalence of this phenomenon is high, but precise figures vary depending on the criteria used to define breakthrough pain and the characteristics of the study population. We found that breakthrough pain usually had the same pathophysiology as the predominant pain and that the vast majority of breakthrough pain was related to direct tumor involvement (77%). Portenoy and Hagen[5] similarly observed that tumor involve-

ment accounted for 75% of breakthrough pain and that 96% of breakthrough pain was located at the site of continuous pain. As in the latter survey,[5] our patients experienced multiple breakthrough pain episodes each day (mean, three). This frequency, combined with the high PI scores before and following the usual breakthrough medication, confirm that breakthrough pain is a significant problem in populations with stable persistent pain.

Most patients in this study (76%) found an effective dose of OTFC. Titration of OTFC from a low initial dose was safe and was associated with typical opioid side effects. There was no meaningful relationship between the fixed schedule opioid dose and the effective OTFC dose. OTFC produced a faster onset of relief and a greater degree of PR than the usual breakthrough medication. Patients rated the global satisfaction of OTFC significantly higher than global satisfaction of their usual breakthrough pain medication.

Current dosing recommendations for breakthrough pain vary, but generally suggest that the effective dose of breakthrough pain medication must be a percentage of a patient's total daily opioid dose. These recommendations have been based on empirical experience and have never been formally studied. The lack of such a relationship in the present controlled titration study suggests that the best dose of OTFC must be determined by titration and is not predicted by total daily opioid dose. Furthermore, morphine equivalency of OTFC has not been determined over the time period relative to the effective treatment of breakthrough pain. The mean successful dose of OTFC used in this study, about 600 μg, approximately corresponds to a mean dose of 18 mg oral morphine predicted by using previously published values for OTFC–intravenous morphine relative potency.[17] However, this reported OTFC–intravenous morphine relationship was calculated using methodology that encompassed several hours of posttreatment observations. In that study, the OTFC–intravenous morphine treatment group differences observed over the first hour, ie, the time period relative to effective treatment of breakthrough pain, were not sufficiently separated to determine the relative potency ratio. This, together with the observation that the regression of the successful dose of OTFC to usual breakthrough pain medication dose in the present study, although correlated, was not proportional, and the lack of correlation between OTFC and patients' total daily opioid dose suggests that using a titration process is better that using a mathematical process to determine proper dosing.

This study was not designed to compare rigorously the usual breakthrough pain medication and OTFC. Although one entry criteria of the study was that patients had to have well-controlled pain, the usual breakthrough medication was not titrated as part of the study. Therefore, the better efficacy of OTFC could relate to suboptimal dose selection for the usual breakthrough drug. Nonetheless, the data indicate that OTFC was effective and well accepted when compared with the usual breakthrough pain medication. Moreover, the data suggest that OTFC has a faster onset of action than oral breakthrough pain medications. At 15 minutes, OTFC produced a PR score that was 131% higher than the score produced with the usual breakthrough pain medication (1.90 *v* 0.82, $P = .0001$). The early onset of analgesia is likely explained by the transmucosal delivery system, which allows rapid absorption of part of the dose. Because of the open-label nature of this comparison, these results should be considered tentative. Further blinded studies will be needed before it can be concluded that OTFC produces better efficacy than usual breakthrough medications.

It was expected that patients would titrate in an identical fashion regardless of starting dose. If so, if the OTFC requirement varied randomly between those started on the 200-μg dose and those who received the 400-μg dose, then patients starting at 400 μg should have been one titration closer to their final dose. This expectation, which would have suggested a dose-response relationship for OTFC, was not confirmed. Although patients did titrate to approximately the same dose, regardless of starting dose, there was no significant difference in the number of titrations. Several factors may have contributed to the failure to identify this expected dose effect. Because patients who were receiving less than 100 μg/h transdermal fentanyl were assigned to start at the low dose, less than half of the patients (29 of 62) were actually randomized into different starting dose groups. In addition, the randomization may not have produced well-matched groups. Specifically, patients randomized to the 400-μg starting dose appeared to have more severe baseline pain than patients randomized to the 200-μg starting dose. First, patients randomized to the 400-μg dose group had a mean usual breakthrough medication dose of 28 mg per episode compared with a mean dose of 15 mg for patients randomized to the 200-μg starting dose ($P = .08$). Second, mean PI scores immediately before OTFC administration were 6.8 for the 400-μg starting dose group, compared with 5.9 for the 200-μg starting dose group ($P = .07$). Third, the severity of pain in the 24-hour period before the start of the study in the 200-μg starting dose group was 3.6, whereas in the 400-μg starting dose group, it was 4.7 ($P = .09$). Given these considerations, the present study cannot clarify the dose-response relationship of OTFC. Additional studies with different methodologies will be needed to accomplish this.

OTFC was well tolerated. Somnolence, nausea, and dizziness were the most common side effects. There were no

reports of respiratory depression, as expected in a population with substantial prior opioid exposure.

In summary, our study evaluated the outcomes associated with the titration of OTFC during treatment of breakthrough pain in cancer patients using transdermal fentanyl. It represents one of the first attempts to apply clinical trials methodology to the study of an intervention for the common problem of breakthrough pain. The data suggest that OTFC is a safe and effective treatment for the management of breakthrough pain in patients with cancer.

APPENDIX

Additional participating institutions include the following: Missouri Baptist Cancer Center, St. Louis, MO (Alan Lyss, MD); Arizona Clinical Research Center, Tucson, AZ (Patricia Plezia, PharmD, and Manuel Modiano, MD); Yale University, New Haven, CT (Lloyd Saberski, MD); North Shore University Hospital, Manhasset, NY (Michael Schuster, MD); The Graduate Hospital, Philadelphia, PA (Arthur Staddon, MD); and Duke University Medical Center, Durham, NC (Eric Winer, MD).

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***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.**

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

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