

1
2 **ACTIQ[®]**
3 **(oral transmucosal fentanyl citrate)**
4

CII

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

7
8 **ACTIQ is indicated only for the management of breakthrough cancer pain in patients with**
9 **malignancies who are already receiving and who are tolerant to opioid therapy for their**
10 **underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking
11 at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of
12 oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another
13 opioid for a week or longer.

14
15 Because life-threatening hypoventilation could occur at any dose in patients not taking chronic
16 opiates, ACTIQ is contraindicated in the management of acute or postoperative pain. This
17 product **must not** be used in opioid non-tolerant patients.

18
19 ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and
20 pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat
21 cancer pain.

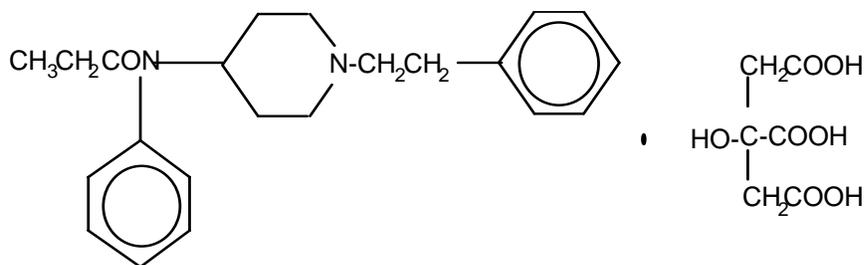
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23 **Patients and their caregivers must be instructed that ACTIQ contains a medicine in an**
24 **amount which can be fatal to a child. Patients and their caregivers must be instructed to**
25 **keep all units out of the reach of children and to discard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

27
28 ***DESCRIPTION***

29
30 ACTIQ (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent
31 opioid analgesic, intended for oral transmucosal administration. ACTIQ is formulated as a white
32 to off-white solid drug matrix on a handle that is fracture resistant (ABS plastic) under normal
33 conditions when used as directed.

34
35 ACTIQ is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal
36 absorption. The handle allows the ACTIQ unit to be removed from the mouth if signs of
37 excessive opioid effects appear during administration.

38
39 **Active Ingredient:** Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate
40 (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is
41 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The
42 molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary
43 nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

6
7 **Inactive Ingredients:** Isomalt, polyethylene glycol 8000, citric acid, dibasic sodium phosphate,
8 artificial berry flavor, magnesium stearate, and edible glue (modified food starch and
9 confectioner's sugar).

10

11 ***CLINICAL PHARMACOLOGY AND PHARMACOKINETICS***

12

13 **Pharmacology:**

14 Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members
15 of the class known as opioid agonists include substances such as morphine, oxycodone,
16 hydromorphone, codeine, and hydrocodone. Pharmacological effects of opioid agonists include
17 anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and
18 cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses
19 there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics,
20 where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist
21 analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed
22 only by side effects, the more serious of which may include somnolence and respiratory
23 depression.

24

25 **Central Nervous System**

26 The precise mechanism of the analgesic action is unknown although fentanyl is known to be a
27 mu opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with
28 opioid-like activity have been identified throughout the brain and spinal cord and play a role in
29 the analgesic effects of this drug.

30 Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The
31 respiratory depression involves both a reduction in the responsiveness of the brain stem to
32 increases in carbon dioxide and to electrical stimulation.

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

35 Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but
36 are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce
37 similar findings).

1 **Gastrointestinal System**

2 Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the
3 antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine
4 and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are
5 decreased, while tone may be increased to the point of spasm resulting in constipation. Other
6 opioid induced-effects may include a reduction in gastric, biliary and pancreatic secretions,
7 spasm of the sphincter of Oddi, and transient elevations in serum amylase.
8

9 **Cardiovascular System**

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

13 **Endocrine System**

14 Opioid agonists have been shown to have a variety of effects on the secretion of hormones.
15 Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They
16 also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and
17 glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has
18 been shown to be both inhibited and stimulated by opioids.
19
20

21 **Clinical Pharmacology**

22 **Analgesia:**

23 The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is
24 made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life).
25 In general, the minimum effective concentration and the concentration at which toxicity occurs
26 rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies
27 widely among individuals. As a result, the dose of ACTIQ should be individually titrated to
28 achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).
29

30 **Gastrointestinal (GI) Tract and Other Smooth Muscle:**

31 Opioids increase the tone and decrease contractions of the smooth muscle of the gastrointestinal
32 (GI) tract. This results in prolongation in GI transit time and may be responsible for the
33 constipating effect of opioids. Because opioids may increase biliary tract pressure, some patients
34 with biliary colic may experience worsening of pain.
35

36 While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends
37 to vary, in some cases producing urinary urgency, in others, difficulty in urination.
38

39 **Respiratory System:**

40 All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory
41 depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy
42 who develop tolerance to respiratory depression and other opioid effects. During the titration
43 phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did
44 increase in patients who were treated with higher doses of ACTIQ. Typically, peak respiratory
45 depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral
46 transmucosal fentanyl citrate (OTFC[®]) administration and may persist for several hours.
47

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

3
4 Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with
5 ACTIQ in clinical trials, fentanyl given rapidly by intravenous injection in large doses may
6 interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians
7 and other healthcare providers should be aware of this potential complication.

8
9 **(See BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,**
10 **ADVERSE REACTIONS, and OVERDOSAGE for additional information on**
11 **hypoventilation.)**

12 13 **Pharmacokinetics**

14 **Absorption:**

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

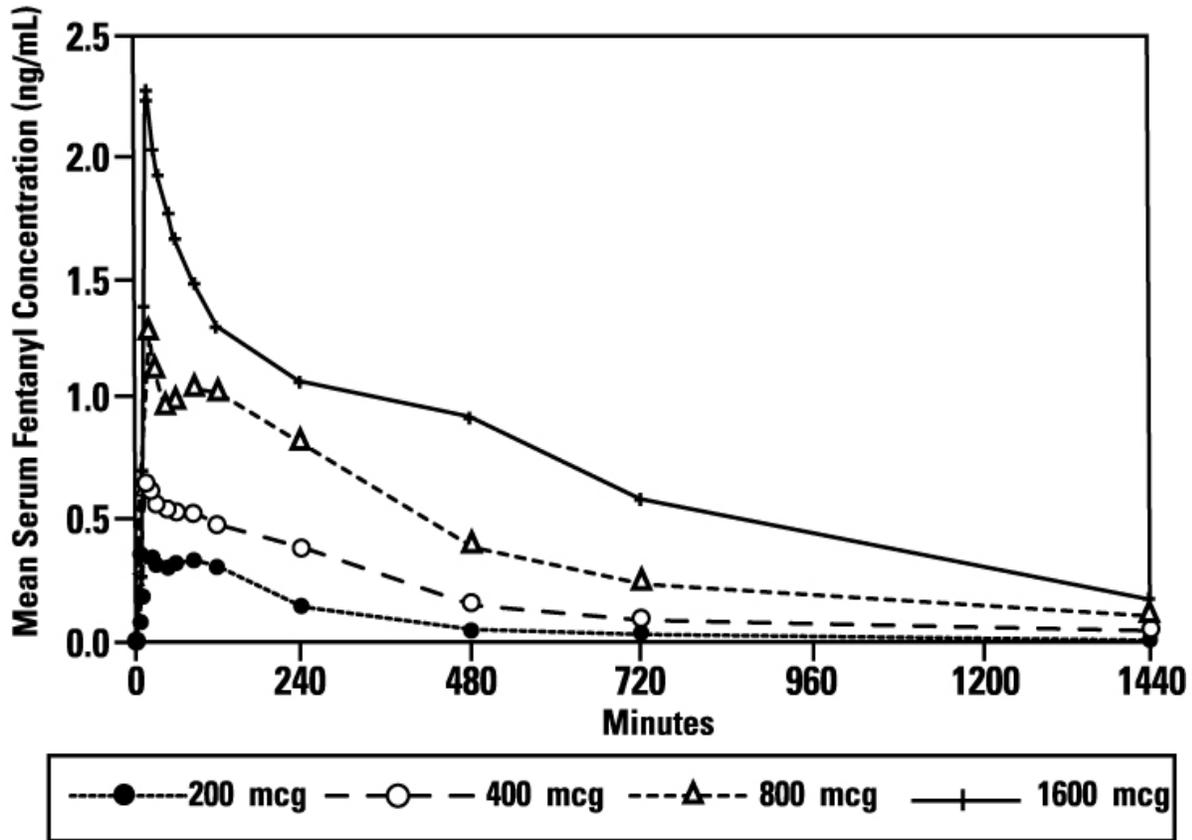
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21 Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg
22 in 12 adult males was 50% compared to intravenous fentanyl.

23
24 Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal
25 mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed
26 with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of
27 the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically
28 available. Thus, the generally observed 50% bioavailability of ACTIQ is divided equally
29 between rapid transmucosal and slower GI absorption. Therefore, a unit dose of ACTIQ, if
30 chewed and swallowed, might result in lower peak concentrations and lower bioavailability than
31 when consumed as directed.

32
33 Dose proportionality among four of the available strengths of ACTIQ (200, 400, 800, and 1600
34 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum
35 fentanyl levels following these four doses of ACTIQ are shown in Figure 1. The curves for each
36 dose level are similar in shape with increasing dose levels producing increasing serum fentanyl
37 levels. C_{max} and $AUC_{0 \rightarrow \infty}$ increased in a dose-dependent manner that is approximately
38 proportional to the ACTIQ administered.

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



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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.

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Table 1.
Pharmacokinetic Parameters* in Adult Subjects
Receiving 200, 400, 800, and 1600 mcg
Units of ACTIQ

Pharmacokinetic Parameter	200 mcg	400 mcg	800mcg	1600 mcg
T_{max}, minute median (range)	40 (20-120)	25 (20-240)	25 (20-120)	20 (20-480)
C_{max}, ng/mL mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC₀₋₁₄₄₀, ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)
t_{1/2}, minute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

7 * Based on arterial blood samples.

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Distribution:

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

16

Metabolism:

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

20

Elimination:

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

27
28

1 **Special Populations:**

2 Elderly Patients:

3 Elderly patients have been shown to be twice as sensitive to the effects of fentanyl when
4 administered intravenously, compared with the younger population. While a formal study
5 evaluating the safety profile of ACTIQ in the elderly population has not been performed, in the
6 257 opioid tolerant cancer patients studied with ACTIQ, approximately 20% were over age 65
7 years. No difference was noted in the safety profile in this group compared to those aged less
8 than 65 years, though they did titrate to lower doses than younger patients (see
9 **PRECAUTIONS**).

10
11 Patients with Renal or Hepatic Impairment:

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

15
16 Although fentanyl kinetics are known to be altered in both hepatic and renal disease due to
17 alterations in metabolic clearance and plasma proteins, individualized doses of ACTIQ have
18 been used successfully for breakthrough cancer pain in patients with hepatic and renal disorders.
19 The duration of effect for the initial dose of fentanyl is determined by redistribution of the drug,
20 such that diminished metabolic clearance may only become significant with repeated dosing or
21 with excessively large single doses. For these reasons, while doses titrated to clinical effect are
22 recommended for all patients, special care should be taken in patients with severe hepatic or
23 renal disease.

24
25 Gender

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

29
30 ***CLINICAL TRIALS***

31
32 **Breakthrough Cancer Pain:**

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

39
40 In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-
41 acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful
42 dose of ACTIQ to treat their breakthrough cancer pain within the dose range offered (200, 400,
43 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events
44 and 14% withdrew due to other reasons. A “successful” dose was defined as a dose where one
45 unit of ACTIQ could be used consistently for at least two consecutive days to treat breakthrough
46 cancer pain without unacceptable side effects.

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

4
5 A double-blind placebo controlled crossover study was performed in cancer patients to evaluate
6 the effectiveness of ACTIQ for the treatment of breakthrough cancer pain. Of 130 patients who
7 entered the study 92 patients (71%) achieved a successful dose during the titration phase. The
8 distribution of successful doses is shown in Table 2.

9
10 **Table 2.**
11 **Successful Dose of ACTIQ**
12 **Following Initial Titration**

<u>ACTIQ Dose</u>	<u>Total No (%)</u> <u>(N=92)</u>
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

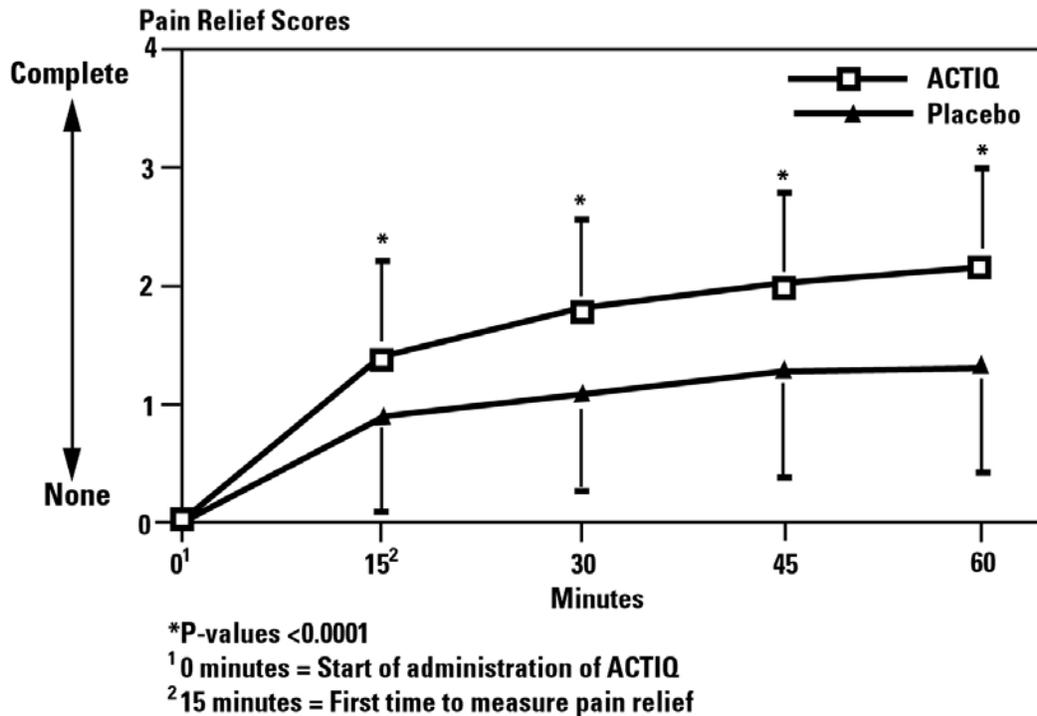
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26 On average, patients over 65 years of age titrated to a mean dose that was about 200 mcg less
27 than the mean dose to which younger adult patients were titrated.

28
29 ACTIQ was administered beginning at Time 0 minutes and produced more pain relief compared
30 with placebo at 15, 30, 45 and 60 minutes as measured after the start of administration (see
31 Figure 2). The differences were statistically significant.

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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)



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INDICATIONS AND USAGE

(See **BOXED WARNING** and **CONTRAINDICATIONS**)

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

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

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

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

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

4 5 **CONTRAINDICATIONS**

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

9
10 Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least
11 25 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or
12 longer.

13
14 ACTIQ is contraindicated in patients with known intolerance or hypersensitivity to any of its
15 components or the drug fentanyl.

16 17 **WARNINGS**

18 **See BOXED WARNING**

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

24
25 ACTIQ is not recommended for use in patients who have received MAO inhibitors within 14
26 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with
27 opioid analgesics.

28
29 **Pediatric Use:** The appropriate dosing and safety of ACTIQ in opioid tolerant children with
30 breakthrough cancer pain have not been established below the age of 16 years.

31
32 **Patients and their caregivers must be instructed that ACTIQ contains a medicine in an**
33 **amount which can be fatal to a child.** Patients and their caregivers must be instructed to keep
34 both used and unused dosage units out of the reach of children. While all units should be
35 disposed of immediately after use, partially consumed units represent a special risk to children.
36 In the event that a unit is not completely consumed it must be properly disposed as soon as
37 possible. (See **SAFETY AND HANDLING, PRECAUTIONS,** and **PATIENT LEAFLET** for
38 specific patient instructions.)

39
40 Physicians and dispensing pharmacists must specifically question patients or caregivers about the
41 presence of children in the home on a full time or visiting basis and counsel them regarding the
42 dangers to children from inadvertent exposure.

1 **PRECAUTIONS**

2 **General**

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

6
7 Opioid analgesics impair the mental and/or physical ability required for the performance of
8 potentially dangerous tasks (e.g., driving a car or operating machinery). Patients taking ACTIQ
9 should be warned of these dangers and should be counseled accordingly.

10
11 The use of concomitant CNS active drugs requires special patient care and observation. (See
12 **WARNINGS**.)

13
14 **Hypoventilation (Respiratory Depression)**

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

19
20 **Chronic Pulmonary Disease**

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

25
26 **Head Injuries and Increased Intracranial Pressure**

27 ACTIQ should only be administered with extreme caution in patients who may be particularly
28 susceptible to the intracranial effects of CO₂ retention such as those with evidence of increased
29 intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a
30 patient with a head injury and should be used only if clinically warranted.

31
32 **Cardiac Disease**

33 Intravenous fentanyl may produce bradycardia. Therefore, ACTIQ should be used with caution
34 in patients with bradyarrhythmias.

35
36 **Hepatic or Renal Disease**

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

40
41 **Information for Patients and Their Caregivers**

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

48

1 The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl)
2 may increase the risk of dental decay. As dental decay in cancer patients may be multifactorial,
3 patients should consult their dentist to ensure appropriate oral hygiene. This ACTIQ formulation
4 contains ISOMALT, a dextrate replacement, and less than 0.05 grams of sugar per unit.
5

6 Patients and their caregivers should be provided with an ACTIQ Welcome Kit, which contains
7 educational materials and safe storage containers to help patients store ACTIQ and other
8 medicines out of the reach of children. Patients and their caregivers should also have an
9 opportunity to watch the patient safety video, which provides proper product use, storage,
10 handling and disposal directions. Patients should also have an opportunity to discuss the video
11 with their health care providers. Health care professionals should call 1-800-505-4421 to obtain a
12 supply of welcome kits or videos for patient viewing.
13

14 **Disposal of Used ACTIQ Units**

15 Patients must be instructed to dispose of completely used and partially used ACTIQ units.
16

- 17 1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the
18 handle in a trash container that is out of the reach of children.
19
- 20 2) If any of the drug matrix remains on the handle, place the handle under hot running tap water
21 until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out
22 of the reach of children.
23
- 24 3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2)
25 at least once a day.
26

27 **If the patient does not entirely consume the unit and the remaining drug cannot be**
28 **immediately dissolved under hot running water, the patient or caregiver must temporarily**
29 **store the ACTIQ unit in the specially provided child-resistant container out of the reach of**
30 **children until proper disposal is possible.**
31

32 **Disposal of Unopened ACTIQ Units When No Longer Needed**

33 Patients and members of their household must be advised to dispose of any unopened units
34 remaining from a prescription as soon as they are no longer needed.
35

36 To dispose of the unused ACTIQ units:
37

- 38 1) Remove the ACTIQ unit from its blister package using scissors, and hold the ACTIQ by its
39 handle over the toilet bowl.
40
- 41 2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
42
- 43 3) Dispose of the handle in a place that is out of the reach of children.
44
- 45 4) Repeat steps 1, 2, and 3 for each ACTIQ unit. Flush the toilet twice after 5 units have been
46 cut and deposited into the toilet.
47

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

4
5 Detailed instructions for the proper storage, administration, disposal, and important instructions
6 for managing an overdose of ACTIQ are provided in the ACTIQ Patient Leaflet. Patients should
7 be encouraged to read this information in its entirety and be given an opportunity to have their
8 questions answered.

9
10 In the event that a caregiver requires additional assistance in disposing of excess unusable units
11 that remain in the home after a patient has expired, they should be instructed to call the toll-free
12 number (1-800-896-5855) or seek assistance from their local DEA office.

13 14 **Laboratory Tests**

15 The effects of ACTIQ on laboratory tests have not been evaluated.

16 17 **Drug Interactions**

18 See **WARNINGS**.

19
20 Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450
21 3A4 isoform. Drugs that inhibit P450 3A4 activity may increase the bioavailability of swallowed
22 fentanyl (by decreasing intestinal and hepatic first pass metabolism) and may decrease the
23 systemic clearance of fentanyl. The expected clinical results would be increased or prolonged
24 opioid effects. Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.
25 However, no *in vitro* or *in vivo* studies have been performed to assess the impact of those
26 potential interactions on the administration of ACTIQ. Thus patients who begin or end therapy
27 with potent inhibitors of CYP450 3A4 such as macrolide antibiotics (e.g., erythromycin), azole
28 antifungal agents (e.g., ketoconazole and itraconazole), and protease inhibitors (e.g., ritonavir)
29 while receiving ACTIQ should be monitored for a change in opioid effects and, if warranted, the
30 dose of ACTIQ should be adjusted.

31 32 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

33 No carcinogenicity studies have been conducted in animals with fentanyl citrate. Isomalt
34 administered up to 10% in the diet of rats and mice was not carcinogenic. Fentanyl citrate was
35 not mutagenic in the *in vitro* Ames reverse mutation assay or the mouse lymphoma mutagenesis
36 assay, and was not clastogenic in the *in vivo* mouse micronucleus assay. Isomalt was not
37 mutagenic in the *in vitro* Ames reverse mutation assay.

38
39 Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg
40 subcutaneously. Isomalt did not affect fertility in rats when administered as 10% of the diet.

41 42 **Pregnancy - Category C**

43
44 No epidemiological studies of congenital anomalies in infants born to women treated with
45 fentanyl during pregnancy have been reported.

46
47 Fentanyl has been shown to increase resorptions in rats when given during organogenesis on
48 gestation days 12 through 21 at IV doses of 30 mcg/kg or subcutaneous doses of 160 mcg/kg.

1 The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse,
2 and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500
3 mcg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted
4 microosmotic minipups did not produce any evidence of teratogenicity (the high dose is
5 approximately 3-times the human dose of 1600 mcg every 6 hours on a mg/m² basis.). In
6 contrast, the intravenous administration of fentanyl (0, 10, or 30 mcg/kg) to bred female rats
7 from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean
8 delivery time in the 30 mcg/kg/day group. There was no clear evidence of teratogenicity noted.
9

10 Pregnant female New Zealand white rabbits were treated with fentanyl (0, 25, 100, 400mcg/kg)
11 via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease
12 in the body weight of the live fetuses at the high dose, which may be attributed to maternal
13 toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse
14 effects on embryo-fetal development at doses up to 400 mcg/kg (approximately 5-times the
15 human dose of 1600 mcg every 6 hours on a mg/m² basis).
16

17 Isomalt did not affect embryo-fetal development in rats or rabbits when administered as 10% of
18 the diet.
19

20 There are no adequate and well-controlled studies in pregnant women. ACTIQ should be used
21 during pregnancy only if the potential benefit justifies the potential risk to the fetus.
22

23 **Labor and Delivery**

24 ACTIQ is not indicated for use in labor and delivery.
25

26 **Nursing Mothers**

27 Fentanyl is excreted in human milk; therefore ACTIQ should not be used in nursing women
28 because of the possibility of sedation and/or respiratory depression in their infants. It is not
29 known whether Isomalt is excreted in human breast milk.
30

31 **Pediatric Use**

32 **See WARNINGS.**
33

34 **Geriatric Use**

35 Of the 257 patients in clinical studies of ACTIQ in breakthrough cancer pain, 61 (24%) were 65
36 years of age and older, while 15 (6%) were 75 years of age and older.
37

38 Those patients over the age of 65 years titrated to a mean dose that was about 200 mcg less than
39 the mean dose titrated to by younger patients. Previous studies with intravenous fentanyl showed
40 that elderly patients are twice as sensitive to the effects of fentanyl as the younger population.
41

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

1 ***ADVERSE REACTIONS***

2 Pre-Marketing Clinical Trial Experience

3 The safety of ACTIQ has been evaluated in 257 opioid tolerant chronic cancer pain patients. The
4 duration of ACTIQ use varied during the open-label study. Some patients were followed for over
5 21 months. The average duration of therapy in the open-label study was 129 days.

6
7 The adverse events seen with ACTIQ are typical opioid side effects. Frequently, these adverse
8 events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated
9 to the proper dose. Opioid side effects should be expected and managed accordingly.

10
11 The most serious adverse effects associated with all opioids are respiratory depression
12 (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and
13 shock. All patients should be followed for symptoms of respiratory depression.

14
15 Because the clinical trials of ACTIQ were designed to evaluate safety and efficacy in treating
16 breakthrough cancer pain, all patients were also taking concomitant opioids, such as sustained-
17 release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data
18 presented here reflect the actual percentage of patients experiencing each adverse effect among
19 patients who received ACTIQ for breakthrough cancer pain along with a concomitant opioid for
20 persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids,
21 duration of ACTIQ therapy, or cancer-related symptoms. Adverse events are included regardless
22 of causality or severity.

23
24 Three short-term clinical trials with similar titration schemes were conducted in 257 patients
25 with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The
26 goal of titration in these trials was to find the dose of ACTIQ that provided adequate analgesia
27 with acceptable side effects (successful dose). Patients were titrated from a low dose to a
28 successful dose in a manner similar to current titration dosing guidelines. Table 3 lists by dose
29 groups, adverse events with an overall frequency of 1% or greater that occurred during titration
30 and are commonly associated with opioid administration or are of particular clinical interest. The
31 ability to assign a dose-response relationship to these adverse events is limited by the titration
32 schemes used in these studies. Adverse events are listed in descending order of frequency within
33 each body system.

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Table 3.
Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Titration (Events in 1% or More of Patients)

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

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

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

- Body as a Whole:** Pain, fever, abdominal pain, chills, back pain, chest pain, infection
- Cardiovascular:** Migraine
- Digestive:** Diarrhea, dyspepsia, flatulence

1 **Metabolic and Nutritional:** Peripheral edema, dehydration

2 **Nervous:** Hypesthesia

3 **Respiratory:** Pharyngitis, cough increased

4

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

7

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

9 **Cardiovascular:** Deep thrombophlebitis, hypertension, hypotension

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

12 **Hemic and Lymphatic:** Anemia, leukopenia

13 **Metabolic and Nutritional:** Edema, hypercalcemia, weight loss

14 **Musculoskeletal:** Myalgia, pathological fracture, myasthenia

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

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

19 **Skin and Appendages:** Alopecia, exfoliative dermatitis

20 **Special Senses:** Taste perversion

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

23

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

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Table 4.
Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment (Events in 1% or More of Patients)

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

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

6
7

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

4
5 **Body as a Whole:** Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills,
6 infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal
7 infection, cachexia, cellulitis, malaise, pelvic pain

8 **Cardiovascular:** Deep thrombophlebitis, migraine, palpitation, vascular disorder

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

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

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

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

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

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

21 **Skin and Appendages:** Skin ulcer, alopecia

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

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

26

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

29

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

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

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

37 **Hemic and Lymphatic:** Bleeding time increased

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

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

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

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

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

47 **Special Senses:** Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness,
48 partial transitory deafness

49 **Urogenital:** Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

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Post-Marketing Experience

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

The following adverse reactions were identified during postapproval use of the ACTIQ formulations that contained approximately 2 grams of sugar per unit:

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 overdose 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.

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

2 Ventilatory support should be provided, intravenous access obtained, and naloxone or other
3 opioid antagonists should be employed as clinically indicated. The duration of respiratory
4 depression following overdose may be longer than the effects of the opioid antagonist's action
5 (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be
6 necessary. Consult the package insert of the individual opioid antagonist for details about such
7 use.
8

9 **Treatment of Overdose in Opioid-Tolerant Patients**

10 Ventilatory support should be provided and intravenous access obtained as clinically indicated.
11 Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but
12 it is associated with the risk of precipitating an acute withdrawal syndrome.
13

14 **General Considerations for Overdose**

15 Management of severe ACTIQ overdose includes: securing a patent airway, assisting or
16 controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or
17 activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or
18 apnea, ventilation should be assisted or controlled and oxygen administered as indicated.
19

20 Patients with overdose should be carefully observed and appropriately managed until their
21 clinical condition is well controlled.
22

23 Although muscle rigidity interfering with respiration has not been seen following the use of
24 ACTIQ, this is possible with fentanyl and other opioids. If it occurs, it should be managed by the
25 use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a
26 neuromuscular blocking agent.
27

28 ***DOSAGE AND ADMINISTRATION***

29 **ACTIQ is contraindicated in non-opioid tolerant individuals.**
30

31 ACTIQ should be individually titrated to a dose that provides adequate analgesia and minimizes
32 side effects (see **Dose Titration**).
33

34 As with all opioids, the safety of patients using such products is dependent on health care
35 professionals prescribing them in strict conformity with their approved labeling with respect to
36 patient selection, dosing, and proper conditions for use.
37

38 Physicians and dispensing pharmacists must specifically question patients and caregivers about
39 the presence of children in the home on a full time or visiting basis and counsel accordingly
40 regarding the dangers to children of inadvertent exposure to ACTIQ.
41

42 **Administration of ACTIQ**

43 The blister package should be opened with scissors immediately prior to product use. The patient
44 should place the ACTIQ unit in his or her mouth between the cheek and lower gum, occasionally
45 moving the drug matrix from one side to the other using the handle. The ACTIQ unit should be
46 sucked, not chewed. A unit dose of ACTIQ, if chewed and swallowed, might result in lower peak
47 concentrations and lower bioavailability than when consumed as directed.
48

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

5
6 **Patients and caregivers must be instructed that ACTIQ contains medicine in an amount**
7 **that could be fatal to a child.** While all units should be disposed of immediately after use,
8 partially used units represent a special risk and must be disposed of as soon as they are consumed
9 and/or no longer needed. Patients and caregivers should be advised to dispose of any units
10 remaining from a prescription as soon as they are no longer needed (see **Disposal Instructions**).

11 **Dose Titration**

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

16
17
18 From this initial dose, patients should be closely followed and the dosage level changed until the
19 patient reaches a dose that provides adequate analgesia using a single ACTIQ dosage unit per
20 breakthrough cancer pain episode.

21
22 Patients should record their use of ACTIQ over several episodes of breakthrough cancer pain and
23 review their experience with their physicians to determine if a dosage adjustment is warranted.

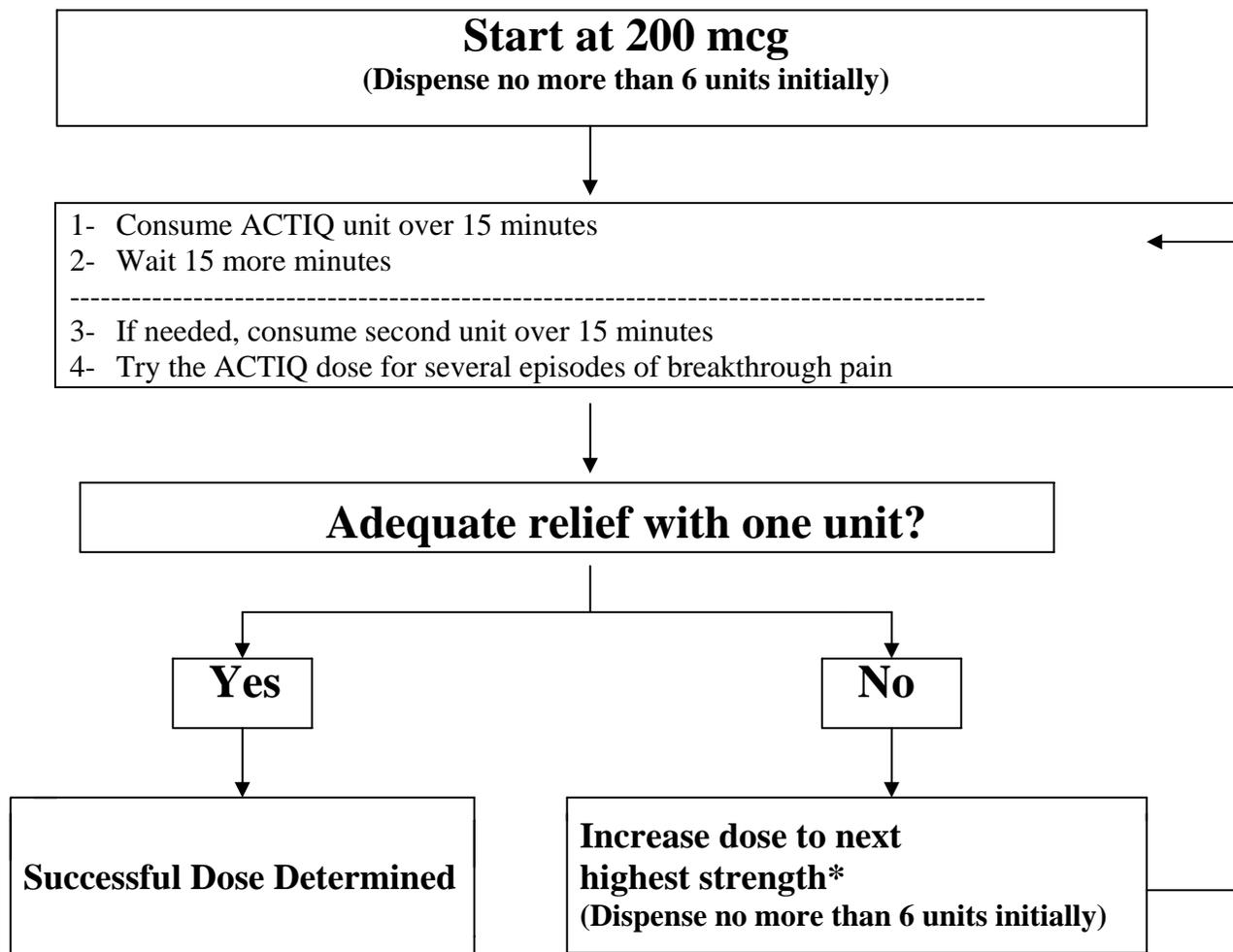
24
25 Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it
26 necessary to use an additional ACTIQ unit during a single episode. Redosing may start 15
27 minutes after the previous unit has been completed (30 minutes after the start of the previous
28 unit). While patients are in the titration phase and consuming units which individually may be
29 subtherapeutic, no more than two units should be taken for each individual breakthrough cancer
30 pain episode.

31
32 Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes
33 requires more than one ACTIQ per episode, an increase in dose to the next higher available
34 strength should be considered. At each new dose of ACTIQ during titration, it is recommended
35 that six units of the titration dose be prescribed. Each new dose of ACTIQ used in the titration
36 period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2
37 days) to determine whether it provides adequate efficacy with acceptable side effects. The
38 incidence of side effects is likely to be greater during this initial titration period compared to
39 later, after the effective dose is determined.

40
41 Daily Limit: Once a successful dose has been found (i.e., an average episode is treated with a
42 single unit), patients should limit consumption to four or fewer units per day. If consumption
43 increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain
44 should be re-evaluated.

ACTIQ Titration Process

See **BOXED WARNING**



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

Dosage Adjustment

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

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

1 **Discontinuation of ACTIQ**

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

5
6 ***SAFETY AND HANDLING***

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

11
12 Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until
13 ready to use. (See USP Controlled Room Temperature.)

14
15 ACTIQ should be protected from freezing and moisture. Do not use if the blister package has
16 been opened.

17
18 ***DISPOSAL OF ACTIQ***

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

24
25 A temporary storage bottle is provided as part of the ACTIQ Welcome Kit (see **Information for**
26 **Patients and Their Caregivers**). This container is to be used by patients or their caregivers in
27 the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of
28 this container are included in the patient leaflet.

29
30 Patients and members of their household must be advised to dispose of any units remaining from
31 a prescription as soon as they are no longer needed. Instructions are included in **Information for**
32 **Patients and Their Caregivers** and in the patient leaflet. If additional assistance is required,
33 referral to the ACTIQ 800# (1-800-896-5855) should be made.

34
35 ***HOW SUPPLIED***

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

39
40 Patients should be prescribed an initial titration supply of six 200 mcg ACTIQ units. At each
41 new dose of ACTIQ during titration, it is recommended that only six units of the next higher
42 dose be prescribed.

43
44 Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on
45 the solid drug matrix, the handle tag, the blister package and the carton. See blister package and
46 carton for product information.

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Dosage Strength (fentanyl base)	Carton/Blister Package Color	NDC Number
--	---	-------------------

200 mcg	Gray	NDC 63459-522-30
400 mcg	Blue	NDC 63459-524-30
600 mcg	Orange	NDC 63459-526-30
800 mcg	Purple	NDC 63459-528-30
1200 mcg	Green	NDC 63459-532-30
1600 mcg	Burgundy	NDC 63459-536-30

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

Rx only.

DEA order form required. A Schedule CII narcotic.

Manufactured by:

Cephalon, Inc., Salt Lake City, UT 84116

U. S. Patent No. 4,671,953; 4,863,737; and 5,785,989

Printed in USA

Label code XXX Date

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ACTIQ[®]

CII

(oral transmucosal fentanyl citrate)



WARNING: Keep out of the reach of children

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

ACTIQ contains medicine that could be harmful or fatal to a child. You MUST keep ACTIQ out of the reach of children. Explain to children that ACTIQ is a medicine for your use only. **ACTIQ can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines on a regular schedule to relieve chronic cancer pain.** If you have not been taking these types of medicines, do not use ACTIQ because it may cause your breathing to slow down to a dangerous level or even to stop. Before starting to use ACTIQ, you should have been using at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer. If you have any questions, ask your doctor.

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

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

If someone accidentally takes ACTIQ:

If the person is not awake and alert, call 911 or call for emergency help immediately.

If the person is awake and alert, call Poison Control at 1-800-690-3924.



WARNING: Keep out of the reach of children

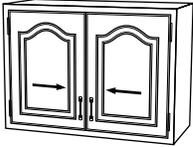
Important Information For People Who Have Children In The Home: You MUST keep ACTIQ out of the reach of children. ACTIQ contains medicine that could be harmful or fatal to a child. Please pay close attention to the child warnings in this patient leaflet.

How to use the ACTIQ Welcome Kit

You have been prescribed an ACTIQ Welcome Kit to help you store ACTIQ and your other medicines out of the reach of children. It is very important that you use the items in the ACTIQ Welcome Kit to protect the children in your home.

Child-resistant lock

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



Portable locking pouch

You may keep a small supply of ACTIQ in the portable locking pouch so that it is nearby for your immediate use. The rest of your ACTIQ must be kept in the locked storage space. Keep this pouch secured with its lock and keep it out of the reach and sight of children.



Child-resistant temporary storage bottle

If for some reason you cannot finish the entire ACTIQ unit and cannot immediately dissolve the medicine under hot tap water, immediately put the ACTIQ in the temporary storage bottle for safe keeping. Push the ACTIQ unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the ACTIQ unit as soon as you can (see How to dispose of ACTIQ after use).



If you did not receive an ACTIQ Welcome Kit, please call 1-800-505-4421.

How to store ACTIQ in your home

- ACTIQ and your other medicines must be stored in a locked storage space. Be sure to use the child-resistant lock that you received in the Welcome Kit.
- Always keep ACTIQ in its blister package until you are ready to use it. Do not use ACTIQ if the blister package has been damaged or opened before you are ready to use it.

- Store ACTIQ at controlled room temperature 68 to 77°F (20-25°C). Do not refrigerate or freeze. Do not store ACTIQ above 77°F (25°C). Remember, the inside of your car can get hot in the summer.

What is ACTIQ?

ACTIQ contains a prescription opioid (narcotic) pain-relieving medicine called fentanyl. When you place ACTIQ in your mouth, it slowly dissolves and the medicine is absorbed through the lining of your mouth. From your mouth, it goes into your bloodstream, where it works to relieve your breakthrough cancer pain.

When to use ACTIQ

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

When not to use ACTIQ

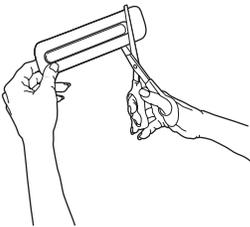
- You should **not** use ACTIQ if you are having short-term pain, including pain from injuries and surgery.
- You should **not** use ACTIQ unless you have breakthrough cancer pain and have been taking a prescription opioid (narcotic) pain medicine every day on a regular schedule. You should have been taking at least 60 mg morphine/day, 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer before beginning use of ACTIQ.

How to use ACTIQ

When you first start using ACTIQ, your doctor will help you find the dose of ACTIQ that will relieve your pain. Use ACTIQ exactly as your doctor or nurse told you to use it. Your doctor will tell you how often you can take ACTIQ safely.



Step 1. Each ACTIQ unit is sealed in its own blister package. **Do not open the package until you are ready to use ACTIQ.** When you are ready to use ACTIQ, cut open the package using scissors and remove the ACTIQ unit.



Step 2. Place ACTIQ in your mouth between your cheeks and gums and actively suck on the medicine. Move ACTIQ around in your mouth, especially along your cheeks. Twirl the handle often.



Finish the ACTIQ completely in 15 minutes to get the most relief. If you finish ACTIQ too quickly, you will swallow more of the medicine and get less relief.



If for some reason you are not finishing the entire unit each time you have an episode of breakthrough cancer pain, you should call your doctor or nurse.

Do not bite or chew ACTIQ. You will get less relief of your breakthrough cancer pain.

If you begin to feel dizzy or sick to your stomach before you have finished the medicine, remove ACTIQ from your mouth. Either dispose of ACTIQ immediately or put it in the temporary storage bottle for later disposal.

You may drink some water before using ACTIQ, but you should not drink or eat anything while using ACTIQ.

How to dispose of ACTIQ after use

Partially used ACTIQ units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed ACTIQ. **You must immediately and properly dispose of the ACTIQ handle after use even if there is little or no medicine left on it.** Please follow these directions to dispose of the handle:

1. If the medicine is totally gone, throw the handle away in a place that is out of the reach of children.
2. If the handle is not totally clean once you are done using ACTIQ, place the handle under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets.



3. If you did not finish the entire ACTIQ unit and you cannot immediately dissolve the medicine under hot running water, put the ACTIQ in the temporary storage bottle that you received in the ACTIQ Welcome Kit for safe keeping. Push the ACTIQ unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partly used ACTIQ units where children or pets can get to them.**
4. Dispose of the handles in the temporary storage bottle as soon as you can by following the directions in steps 1 and 2. You must dispose of all handles in the temporary storage bottle at least once a day.

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

What to expect from ACTIQ

You may begin to feel some pain relief 15 minutes after you start taking ACTIQ. You may not get full relief for up to 45 minutes after you have finished taking ACTIQ. If you do not get enough pain relief from just one ACTIQ, your doctor may allow you to use another one. Do not use a second ACTIQ unless your doctor or nurse tells you that you may do so.

Some people will have side effects with ACTIQ. The most common side effects are feeling sleepy, sick to your stomach, or dizzy. If you begin to feel very sleepy, remove the ACTIQ from your mouth or call another person in your household to help you.

For best results, let your doctor or nurse know about your pain and how ACTIQ is working for you so the dose can be changed, if needed.

Important safety information for patients and caregivers

You and the other people in your home should be aware of some important information about ACTIQ. **Always feel free to contact your doctor or nurse with any questions or concerns you may have about ACTIQ and any side effects.**

- A serious side effect of ACTIQ is slow, shallow breathing. This can occur if your dose of ACTIQ is too high or if you take too much ACTIQ. You and your caregivers should discuss this side effect with your doctor. **Attention Caregivers:** If you see that the person taking ACTIQ has slow breathing or if you have a hard time waking the person up, remove the ACTIQ from their mouth and call for emergency help. (See What to do if a child or an adult accidentally takes ACTIQ.)
- ACTIQ may change the effect of other medicines (prescription and over-the-counter). ACTIQ will also add to the effects of alcohol and medicines that make you sleepy (like sleeping pills, anxiety medicines, antihistamines, or tranquilizers). Make sure that you talk to your doctor before drinking alcohol or taking any medicines (other than your regularly scheduled opioid [narcotic] pain medicines) while using ACTIQ.
- ACTIQ may cause some people to become sleepy, dizzy, or less alert. Discuss this with your doctor to get advice on whether it is safe for you to drive or operate machinery. Until you have experienced how this medicine affects you, do not drive a car or operate potentially dangerous machinery. You should discuss this further with your doctor.
- The occurrence of dry mouth associated with the use of opioid medications, such as the fentanyl in ACTIQ, may add to the risk of dental cavities or tooth decay . You should consult your dentist to ensure appropriate dental care while using ACTIQ.
- Do not use ACTIQ if you are pregnant or nursing unless told that you may do so by your doctor.

What to do if a child or an adult accidentally takes ACTIQ

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

1. Remove the ACTIQ unit from the person's mouth.
2. If the person is asleep, wake them and keep them awake by calling their name and shaking their arm or shoulder.
3. **If the person is not awake and alert, call 911 or call for emergency help.** If the person is awake and alert, call Poison Control at 1-800-690-3924.

While waiting for emergency help:

4. If the person seems to be breathing slowly, every 5 to 10 seconds tell them to breathe.
5. If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.

How to know if someone has accidentally taken ACTIQ

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

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

When to call your doctor or nurse

- If you have side effects that bother you and do not go away.
- If you want to take any over-the-counter medicines.
- If another doctor has prescribed any new medicines for you.
- If you do not get enough breakthrough cancer pain relief.
- If you are using ACTIQ more than four times a day.
- If you are not finishing the entire ACTIQ unit.

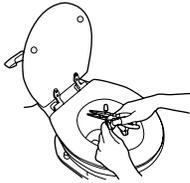
When ACTIQ is no longer needed

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

Step 1. Remove all ACTIQ from the locked storage space.

Step 2. Remove one ACTIQ unit from its blister package using scissors, and hold the ACTIQ by its handle over the toilet bowl.

Step 3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.



Step 4. Throw the handle away in a place that is out of the reach of children.

Step 5. Repeat steps 2, 3, and 4 for each ACTIQ. Flush the toilet twice after 5 ACTIQ units have been cut. Do not flush more than 5 ACTIQ units at a time.

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

If you need help with disposal of ACTIQ, call 1-800-896-5855. If you still need help, call your local Drug Enforcement Administration (DEA) office.



WARNING: Keep out of the reach of children

Manufactured by:

Cephalon, Inc., Salt Lake City, UT 84116.

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