

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**20-747 / S-019**

***Trade Name:***      **Actiq**

***Generic Name:***    **Oral transmucosal fentanyl citrate**

***Sponsor:***            **Cephalon**

***Approval Date:***    **September 9, 2005**

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-747 / S-019**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**APPROVAL LETTER**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-747/S-019

Cephalon, Inc.  
145 Brandywine Parkway  
West Chester, PA 19380-4245

Attention: Carol Marchione  
Senior Director, Regulatory Affairs

Dear Ms. Marchione:

Please refer to your supplemental new drug application dated November 19, 2004, received November 19, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Actiq® (oral transmucosal fentanyl citrate).

We acknowledge receipt of your submissions dated January 28 and 31, March 8, April 13, May 10, and August 9, 2005.

Your submission of May 10, 2005, constituted a complete response to our March 18, 2005, action letter.

This supplemental new drug application provides for a sugar-free formulation of the drug product.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, and for use as recommended in the agreed-upon labeling text with the following minor editorial revision as agreed upon in your email of September 1, 2005.

In Figure 2 of the package insert, change the line from time point 0 to 15 mins to a dashed line.

The final printed labeling (FPL) must be identical, and include the minor editorial revision indicated, to the enclosed labeling (text for the package insert, text for the patient package insert), and submitted labeling (immediate container and carton labels submitted May 10, 2005). This revision are terms of the approval of this application.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-747/S-019.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your agreements, as per your September 9, 2005, correspondence, to submit a CBE-30 supplement providing for the conduct of crystallinity testing of the isomalt excipient and to market

this sugar-free formulation of the Actiq drug product with an 18-month expiry date for the drug product.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD  
Director  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Bob Rappaport  
9/9/2005 05:54:35 PM

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**20-747 / S-019**

**LABELING**

1  
2 **ACTIQ<sup>®</sup>**  
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.  
22

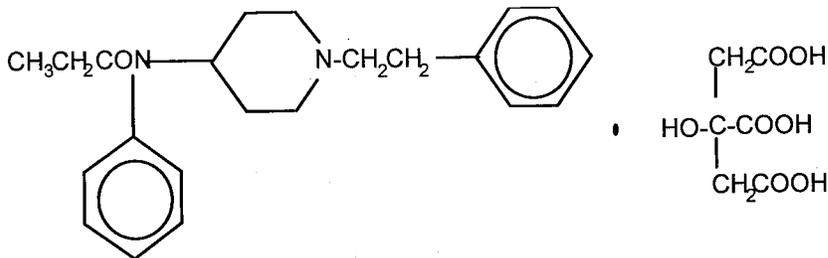
23 **Patients and their caregivers must be instructed that ACTIQ contains a medicine in an**  
24 **amount which can be fatal to a child. Patients and their caregivers must be instructed to**  
25 **keep all units out of the reach of children and to discard opened units properly. (See**  
26 **Information 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:  
44



1  
2  
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<sup>®</sup>) 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.

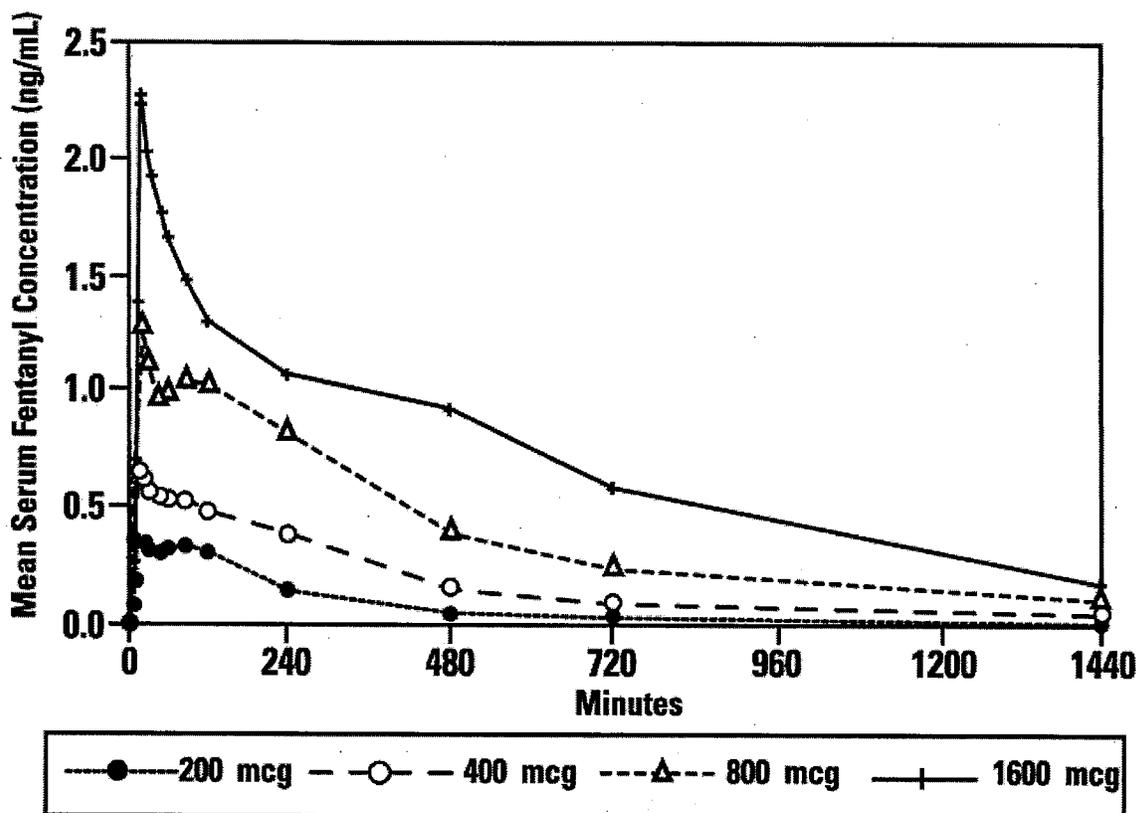
20  
21 Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg  
22 in 12 adult males was 50% compared to intravenous fentanyl.

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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12  
13

The pharmacokinetic parameters of the four strengths of ACTIQ tested in the dose-proportionality study are shown in Table 1. The mean  $C_{max}$  ranged from 0.39 - 2.51 ng/mL. The median time of maximum plasma concentration ( $T_{max}$ ) across these four doses of ACTIQ varied from 20 - 40 minutes (range of 20-480 minutes) as measured after the start of administration.

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

Pharmacokinetic Parameter	200 mcg	400 mcg	800mcg	1600 mcg
<b>T<sub>max</sub>, minute</b> median (range)	40 (20-120)	25 (20-240)	25 (20-120)	20 (20-480)
<b>C<sub>max</sub>, ng/mL</b> mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
<b>AUC<sub>0-1440</sub>,</b> <b>ng/mL minute</b> mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)
<b>t<sub>1/2</sub>, minute</b> mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

\* Based on arterial blood samples.

**Distribution:**

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

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**

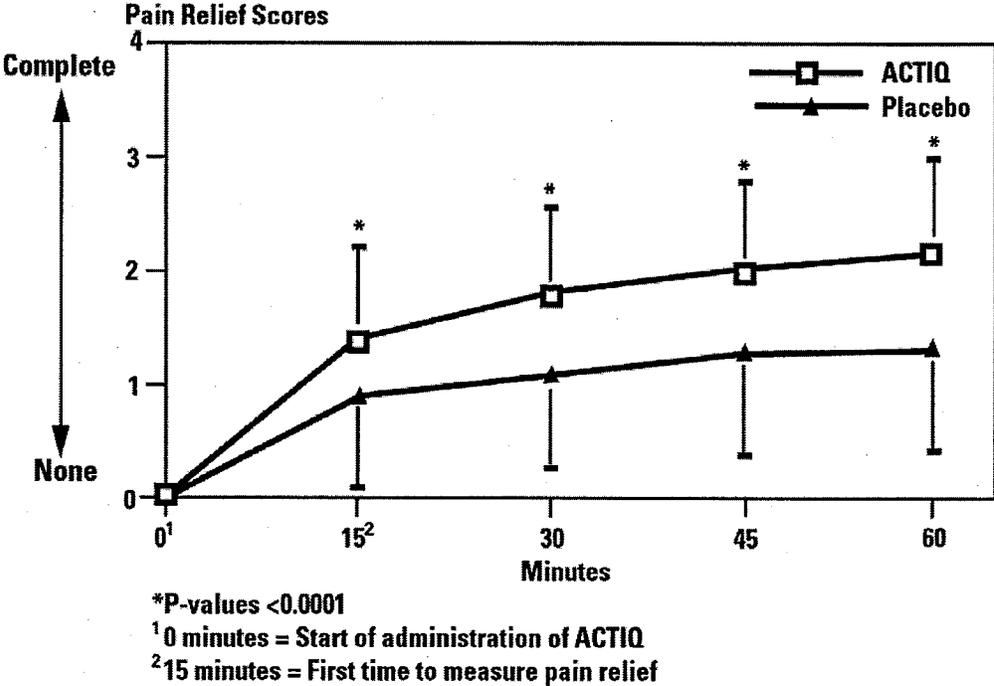
<u>ACTIQ Dose</u>	<u>Total No (%)</u> <u>(N=92)</u>
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean $\pm$ SD	789 $\pm$ 468 mcg

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25  
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 CO<sub>2</sub> 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., ritanovir)  
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 minipumps 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/m<sup>2</sup> 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/m<sup>2</sup> 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.

**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)
<b>Body As A Whole</b>					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2
<b>Digestive</b>					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
<b>Nervous</b>					
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
<b>Respiratory</b>					
Dyspnea	2	3	6	5	4
<b>Skin</b>					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
<b>Special Senses</b>					
Abnormal Vision	1	0	2	0	2

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

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

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

**Cardiovascular:** Migraine

**Digestive:** Diarrhea, dyspepsia, flatulence

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.

1  
2  
3  
4  
5  
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)
<b>Body As A Whole</b>					
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
<b>Digestive</b>					
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
<b>Cardiovascular</b>					
Hypertension	1	1	0	0	1
<b>Nervous</b>					
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
<b>Respiratory</b>					
Dyspnea	15	16	8	7	22
<b>Skin</b>					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
<b>Special Senses</b>					
Abnormal Vision	2	2	0	0	3
<b>Urogenital</b>					
Urinary Retention	1	2	0	0	2

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

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

1  
2 Post-Marketing Experience

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

8  
9 The following adverse reactions were identified during postapproval use of the ACTIQ  
10 formulations that contained approximately 2 grams of sugar per unit:

11  
12       dental decay of varying severity including dental caries, tooth loss, and gum line  
13       erosion

14  
15 **DRUG ABUSE AND DEPENDENCE**

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

18  
19 The administration of ACTIQ should be guided by the response of the patient. Physical  
20 dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer  
21 pain, and fear of tolerance and physical dependence should not deter using doses that adequately  
22 relieve the pain.

23  
24 Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal  
25 symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated  
26 through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmeferne, or  
27 mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

28  
29 Physical dependence usually does not occur to a clinically significant degree until after several  
30 weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in  
31 order to produce the same degree of analgesia, is initially manifested by a shortened duration of  
32 analgesic effect, and subsequently, by decreases in the intensity of analgesia.

33  
34 The handling of ACTIQ should be managed to minimize the risk of diversion, including  
35 restriction of access and accounting procedures as appropriate to the clinical setting and as  
36 required by law (see **SAFETY AND HANDLING**).

37  
38 **OVERDOSAGE**

39 **Clinical Presentation**

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

43  
44 **General**

45 Immediate management of opioid overdose includes removal of the ACTIQ unit, if still in the  
46 mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment  
47 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  
13 Starting Dose: *The initial dose of ACTIQ to treat episodes of breakthrough cancer pain should*  
14 *be 200 mcg.* Patients should be prescribed an initial titration supply of six 200 mcg ACTIQ units,  
15 thus limiting the number of units in the home during titration. Patients should use up all units  
16 before increasing to a higher dose.

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.

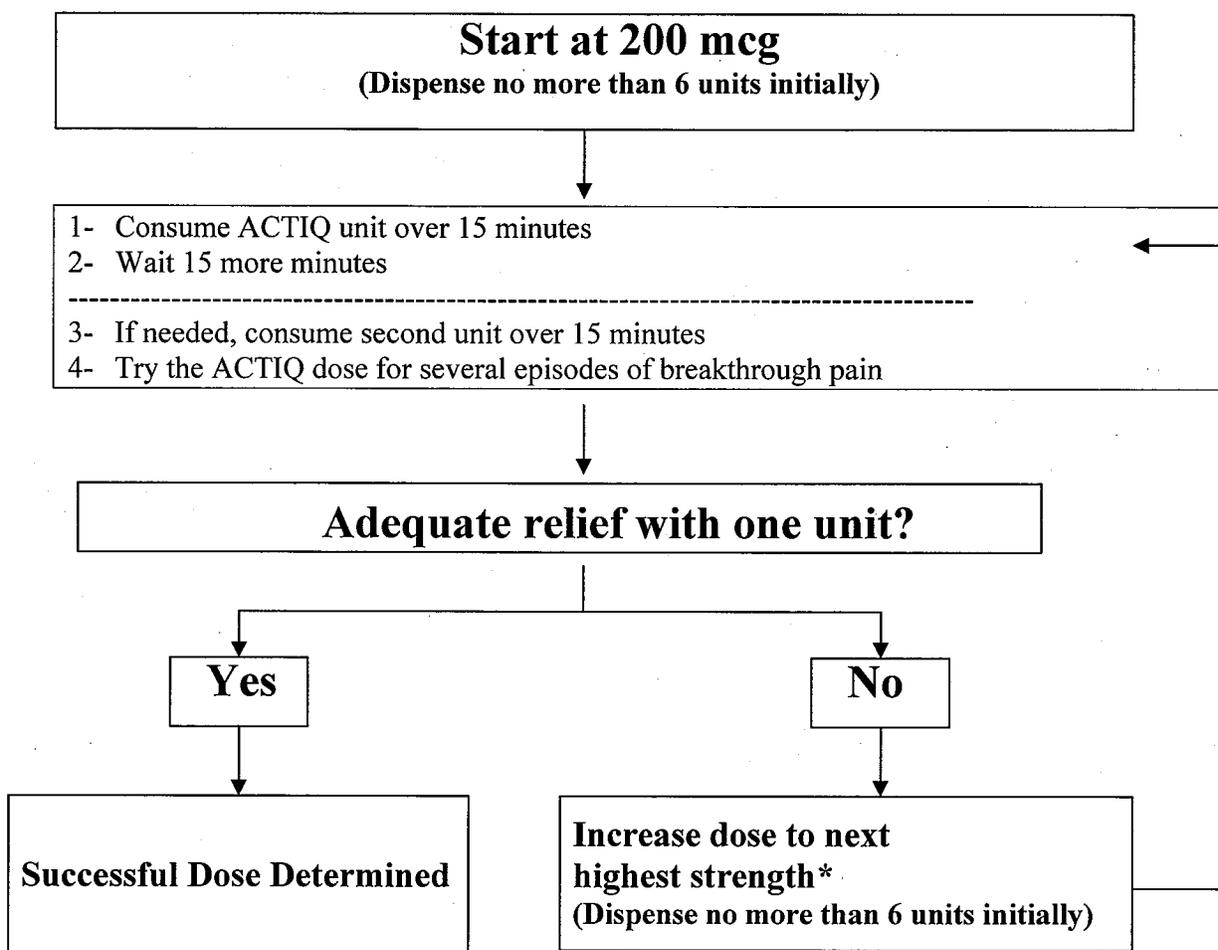
24  
25 Redosing Within a Single Episode: Until the appropriate dose is reached, patients may find it  
26 necessary to use an additional ACTIQ unit during a single episode. Redosing may start 15  
27 minutes after the previous unit has been completed (30 minutes after the start of the previous  
28 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, PRECAUTIONS,**  
10 **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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<b>Dosage Strength (fentanyl base)</b>	<b>Carton/Blister Package Color</b>	<b>NDC Number</b>
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<sup>®</sup>

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**

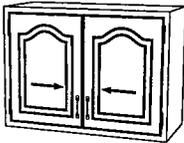
**Important Information For People Who Have Children In The Home:** You MUST keep ACTIQ out of the reach of children. ACTIQ contains medicine that could be harmful or fatal to a child. Please pay close attention to the child warnings in this patient leaflet.

## 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

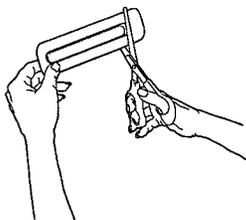
- You should **not** use ACTIQ if you are having short-term pain, including pain from injuries and surgery.
- You should **not** use ACTIQ unless you have breakthrough cancer pain and have been taking a prescription opioid (narcotic) pain medicine every day on a regular schedule. You should have been 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.**

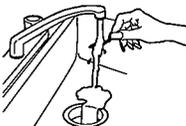
If you begin to feel dizzy or sick to your stomach before you have finished the medicine, remove ACTIQ from your mouth. Either dispose of ACTIQ immediately or put it in the temporary storage bottle for later disposal.

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 1-800-690-8924.

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.

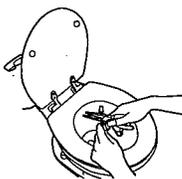
#### When ACTIQ is no longer needed

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.

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

Label code XXXXXXXXXX.XX

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Printed in the USA

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**MEDICAL REVIEW(S)**



**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170, Room 9B-45

**Medical Officer Review**  
**Serial No.: 019**

**NDA: 20-747**  
**Drug Name: ACTIQ**  
**Sponsor: Cephalon**  
**Type of Submission: SLR**  
**Date of Submission: 7 February 2005**  
**Date of Review: 1 March 2005**  
**Reviewer: D. Elizabeth McNeil MD**  
**Team Leader: Rigoberto Roca MD**  
**Project Manager: Kim Compton**

---

**Addendum:**

I had originally added the language on the interaction between ritonavir and fentanyl that was placed in the ~~\_\_\_\_\_~~ to this label in the drug interactions subsection of **PRECAUTIONS**.

Upon further review \_\_\_\_\_

\_\_\_\_\_ The relevant section of the ACTIQ label does warn that patients taking ritonavir and ACTIQ should be monitored for a change in opioid effects.

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/s/

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Dawn McNeil

3/9/05 09:05:37 AM

MEDICAL OFFICER

This is an explanation of a modification made to  
the label after my review was placed in  
DFS.

Rigoberto Roca

3/17/05 11:53:36 AM

MEDICAL OFFICER



**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
Division of Anesthetic, Critical Care, and Addiction Drug Products  
HFD-170, Room 9B-45

**Medical Officer Review**

**NDA: 20-747**

**Serial No.: 019**

**Drug Name: ACTIQ**

**Sponsor: Cephalon**

**Type of Submission: SLR**

**Date of Submission: 7 February 2005**

**Date of Review: 1 March 2005**

**Reviewer: D. Elizabeth McNeil MD**

**Team Leader: Rigoberto Roca MD**

**Project Manager: Kim Compton**

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**Background:**

Cephalon has produced a sugar-free formulation of the currently marketed Actiq. The current label is intended to remove the information on the sugar-containing formulation which is no longer relevant.

Where necessary in the body of this review- the sponsor's proposals will be placed in **bold** text, the FDA proposals will be in plain text and the reviewer comments will be in *italics*.

**LABELING REVIEW for the PI**

**BOX WARNING:**

The sentence describing opioid tolerance has been modified to read "Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 25 mcg transdermal fentanyl/hour, or at least 30 mg of oxycodone daily or at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer."

*Reviewer's note: The transdermal fentanyl dose has been reduced from 50 mcg/hour to 25 mcg/hour throughout the label in order to make this label consistent with the Duragesic and Palladone labels.*

**DESCRIPTION**

The sponsor has deleted hydrated dextrans, modified food starch and confectioner's sugar from the list of inactive ingredients.

The sponsor has removed the language stating that the ACTIQ handle is

*Reviewer's note: The change to the inactive ingredients is appropriate. We have post-marketing data which shows that an aspirated handle was not apparent on x-ray so the removal of the term radioopaque is appropriate.*

## **CLINICAL PHARMACOLOGY**

Clinical pharmacology, analgesia subsection:

The sentence reading "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" has been deleted.

The mention of sedation as a therapeutic benefit has been removed.

*Reviewer's note: We removed the language related to opioid-naïve patients from the Duragesic label as well.*

## **CLINICAL TRIALS**

The sentences describing the pain relief from ACTIQ compared with placebo have been modified to account for the 15 minute administration time. Figure 2 was modified for the same reason.

The patient rating of Actiq performance has been deleted as we do not have sufficient data to determine whether patients are experiencing perceptible or meaningful pain relief. The sentence referring to pain relief in the first 15 minutes (during the administration period) has been removed for the same reason.

## **PRECAUTIONS**

Information for patients and their caregivers subsection:

The language related to the risk of dental decay has been modified and the language regarding the amount of sugar in the current formulation has been clarified.

Drug interactions subsection:

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## **LABELING REVIEW for the PPI**

Information on appropriate past opioid exposure has been added to the boxed warning and the section entitled "When not to use Actiq".

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/s/

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Dawn McNeil  
3/8/05 12:08:57 PM  
MEDICAL OFFICER

Rigoberto Roca  
3/17/05 11:48:42 AM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**CHEMISTRY REVIEW(S)**

<b>Chemistry Review 1</b>	<b>1. Division</b> HFD-170	<b>2. NDA 20-747</b>
<b>3. Name and Address of Applicant</b> Cephalon, Inc. 145 Brandywine Pkwy West Chester, PA 19380-4245 Tel. 610-738-6237, Attn: Carol S. Marchione, Sr. Director Regulatory Affairs		<b>4. Supplement</b> <b>Number      Date</b> SCM-019    11/19/04
<b>5. Name of Drug</b> Actiq Oral Transmucosal Fentanyl Citrate	<b>6. Nonproprietary Name</b> fentanyl citrate lozenge	
<b>7. Supplement Provides for:</b> provides for a new formulation of the drug product... A sugar free formulation.		<b>8. Amendment(s)</b>
<b>9. Pharmacological Category</b> Analgesic, narcotic	<b>10. How Dispensed</b> Rx	<b>11. Related Documents</b>
<b>12. Dosage Form</b> lollipop (lozenge on the stick)	<b>13. Potency(ies):</b> 200, 400, 600, 800, 1200, 1600 µg/lollipop (lozenge)	
<b>14. Chemical Name and Structure</b> see page 2		
<b>15. Comments</b> see page 3		
<b>16. Conclusions and Recommendations</b> It is recommended that approval be withheld to this supplemental application. This supplemental application is approvable pending satisfactory resolution of the deficiencies listed in the draft letter. These deficiencies must be conveyed to the Applicant.  All manufacturing facilities were found acceptable by the Office of Compliance.  CC: NDA 20-747/SCM-019 HFD-170/Division File HFD-170/MTheodorakis HFD-170/KCompton		
<b>17. Name</b> Michael C. Theodorakis, Ph.D. Senior Chemistry Reviewer	<b>Signature</b>	<b>Date</b> <b>6-Mar-2005</b>
Ravi S. Harapanhalli, Ph.D, Chemistry Team Leader		

**WITHHOLD** 68 **PAGE(S)**

Chemistry Review  
B4

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/s/

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Michael Theodorakis  
3/17/05 04:00:54 PM  
CHEMIST

Ravi Harapanhalli  
3/17/05 04:21:42 PM  
CHEMIST

AE (Deficiences). Recommendation on the use of "sugar-free formulation" is being deferred. DMF related to this supplement is inadequate.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 20-747  
SERIAL NUMBER: S-019  
DATE RECEIVED BY CENTER: 11/19/2004  
DRUG NAME: oral transmucosal fentanyl citrate (ACTIQ®)  
INDICATION: 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  
SPONSOR: Cephalon, Inc.  
DOCUMENTS REVIEWED: electronic  
REVIEW DIVISION: Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)  
PHARM/TOX REVIEWER: Suzanne R. Thornton-Jones, Ph.D.  
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.  
DIVISION DIRECTOR: Bob Rappaport, M.D.  
PROJECT MANAGER: Kim Compton

Date of review submission to Division File System (DFS): 11 March 2005

## EXECUTIVE SUMMARY

### I. Recommendations

#### A. Recommendation on acceptability.

The NDA supplement can be approved from a pharmacology/toxicology perspective.

#### B. Recommendation for nonclinical studies.

None.

#### C. Recommendations on labeling.

#### **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

No carcinogenicity studies have been conducted in animals with fentanyl citrate. Isomalt administered up to 10% in the diet of rats and mice was not carcinogenic.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay. Isomalt was not mutagenic in the *in vitro* Ames reverse mutation assay.

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

#### **Pregnancy - Category C**

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

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

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 µg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 3-times the human dose of 1600 mcg every 6 hours on a mg/m<sup>2</sup> basis). In contrast, the intravenous administration of fentanyl (0, 0.01, or 0.03 mg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 5-times the human dose of 1600 mcg every 6 hours on a mg/m<sup>2</sup> basis).

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

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. It is not known whether Isomalt is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIQ is administered to a nursing woman.

## **II. Summary of nonclinical findings**

### **A. Brief overview of nonclinical findings.**

In a dog buccal absorption model, commercial ACTIQ lead to abrasions, while the formulations containing Isomalt did not lead to abrasions but lead to redness. Formulations chosen for the human bioequivalent studies were "B" which is a — (Isomalt/fentanyl) at a pH — and "C" which is — ratio at a pH —

The excipient Isomalt is minimally absorbed, distributed, and metabolized. It is significantly excreted unchanged in the feces. It was also not mutagenic in the Ames assay, carcinogenic in mice or rats, and did not cause reproductive toxicity at doses up to 10% in the diet.

Based upon review of the Mallinckrodt's synthetic scheme for the fentanyl used for this drug product, the Chemistry review team has identified three potential drug substance impurities containing structural alerts for mutagenicity in them.

that the structural alert mutagens are present in the drug substance or drug product.

B. Pharmacologic activity.

Fentanyl citrate is *mu* opioid agonist. Isomalt is an inactive ingredient used as a sweetener that does not alter glucose and insulin levels and is not cariogenic.

C. Nonclinical safety issues relevant to clinical use.

Oral high doses of Isomalt have a laxative effect in man. The dose range where its laxative effect occurs is 20-50 g in adults and 10-40 g in pediatric patients. The amount of Isomalt in the ACTIQ lozenge is 1-5 times below the laxative exerting amounts. Since opioids, such as fentanyl, are known to increase GI tone leading to a decrease in GI motility, the laxative effect may be beneficial in these patients and will likely not be a serious adverse effect. The laxative effect can be monitored in patients prescribed ACTIQ.

Reviewer Signature: Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature: R. Daniel Mellon, Ph.D. Concurrency Yes X No

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**2.6 PHARMACOLOGY/TOXICOLOGY REVIEW****2.6.1 INTRODUCTION AND DRUG HISTORY**

**NDA NUMBER:** 20-747  
**IND NUMBER:** 27,428  
**SEQUENCE NUMBER/DATE/TYPER OF SUBMISSION:** NDA: S-019/19 November 2004  
S-019/08 March 2005/BC  
IND: N444/22 March 2004/IT  
N452/14 October 2004/IT

**INFORMATION TO SPONSOR:** Yes ( ) No (X)  
**SPONSOR:** Cephalon, Inc.  
145 Brandywine Parkway  
West Chester, PA 19380-4245  
Mallinckrodt Inc.

**MANUFACTURER FOR DRUG SUBSTANCE:** Mallinckrodt Inc.  
**REVIEWER NAME:** Suzanne R. Thornton-Jones, Ph.D.  
**DIVISION NAME:** DACCADP  
**HFD #:** 170  
**REVIEW COMPLETION DATE:** 09 March 2005  
**DRUG:**

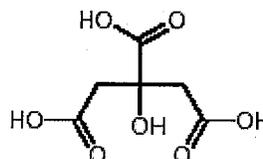
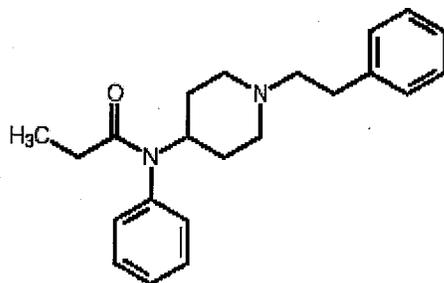
**TRADE NAME:** ACTIQ®  
**GENERIC NAME (LIST ALPHABETICALLY):** fentanyl citrate  
**CODE NAME:** NA  
**CHEMICAL NAME:**  
[Fentanyl citrate] N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate  
[Isomalt] 6-O-alpha-D-Glucopyranosyl-D-sorbitol (1,6-GPS)/  
1-O-alpha-D-Glucopyranosyl-D-mannitol dihydrate (1,1-GPM)

**CAS REGISTRY NUMBER:** [Fentanyl citrate] 990-73-8\  
[Isomalt] 64519-82-0

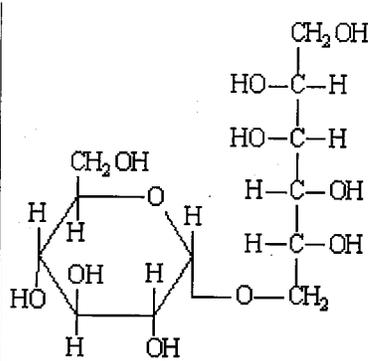
**MOLE FILE NUMBER:** not specified  
**MOLECULAR FORMULA/MOLECULAR WEIGHT:**  
[Fentanyl citrate] C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O • C<sub>6</sub>H<sub>8</sub>O<sub>7</sub>/528.59  
[Isomalt] GPS C<sub>12</sub>H<sub>24</sub>O<sub>11</sub>/344.32  
GPM C<sub>12</sub>H<sub>24</sub>O<sub>11</sub>•2H<sub>2</sub>O/380.32

**STRUCTURE:**

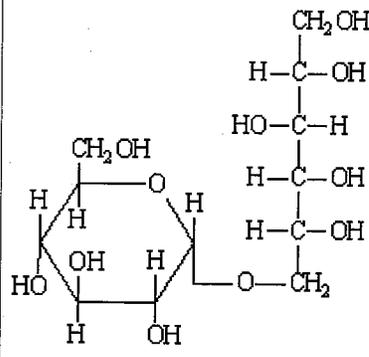
[Fentanyl Citrate]



[Isomalt]



6-O-alpha-D-Glucopyranosyl-D-sorbitol



1-O-alpha-D-Glucopyranosyl-D-mannitol (without molecules of crystal water)

**RELEVANT INDs/NDAs/DMFs:**

**DRUG CLASS:**

**INTENDED CLINICAL POPULATION:**

IND 27,428; DMF \_\_\_\_\_

[Fentanyl citrate] opioid agonist;

[Isomalt] sweetener, \_\_\_\_\_

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

**CLINICAL FORMULATION:**

**Table 3.2.P.1-1: Per Unit Compositions of the 6 Strengths of the Proposed Formulation of ACTIQ**

Ingredient	Function	Standard or grade	Dosage unit formula by strength (fentanyl base)					
			All ingredients in mg					
			200 µg	400 µg	600 µg	800 µg	1200 µg	1600 µg
[Redacted content]								

**ROUTE OF ADMINISTRATION:** oral/transmucosal

**PROPOSED CLINICAL PROTOCOL:** No new clinical studies were submitted.

**BACKGROUND/PREVIOUS CLINICAL EXPERIENCE:** The Sponsor is planning to develop a sugar-free ACTIQ® product to replace the currently approved formulation of ACTIQ® (oral transmucosal fentanyl citrate). The purpose of this reformulation is to provide a sugar-free product that is less likely to cause dental caries or a glycemic response in diabetic patients compared to the current dextrans-based ACTIQ. The currently approved product uses \_\_\_\_\_ and the proposed sugar-free formulation uses Isomalt as a \_\_\_\_\_ and polyethylene glycol (PEG) 8000, NF \_\_\_\_\_. The Sponsor does not intend to change the name of the product to identify the new formulation but will call the sugar free product ACTIQ.

Two formulations were used in a human bioequivalence study based on non-clinical dog study results. These formulations were compared to the current approved formulation. These developmental formulations were designated formulation "A" (\_\_\_\_\_ isomalt/PEG8000, target pH \_\_\_\_\_) and formulation "B" (\_\_\_\_\_ Isomalt/PEG8000, pH \_\_\_\_\_. The results of this study indicated that formulation "A" was bioequivalent to the current approved formulation.

The proposed formulation of sugar-free ACTIQ will be the same six (6) dosage strengths (200, 400, 600, 800, 1200 and 1600 µg) as the current ACTIQ formulation. The fentanyl citrate drug substance and drug substance manufacturer (\_\_\_\_\_) remain unchanged from the currently approved formulation as referenced in NDA 20-747.

Sponsor provides a Letter of Authorization for us to reference DMF \_\_\_\_\_ for Isomalt. Please see the review of the DMF for the toxicology review of Isomalt. Isomalt belongs to the class of disaccharide polyols like maltitol and lactitol. It is derived exclusively from sucrose and consists of two components in a 1:1 ratio, 1,6-glucopyranosyl-D-sorbitol (GPS) and 1,1-

glucopyranosyl-D-mannitol (GPM). Complete hydrolysis of isomalt yields glucose (50%), sorbitol (25%), and mannitol (25%). Isomalt is a unique sweetener because: 1) it is not broken down by oral bacteria because they can not glucose-sorbitol and glucose-mannitol bonds of the GPS and GPM, respectively, therefore it does not cause food decay (anti-cariogenic); 2) only about one-half of the Isomalt is digested and absorbed leading to 50% less calories (2 calories/gram) compared to other sweeteners; and 3) the components are slowly digested and absorbed which does not raise glucose and insulin levels (non-glycemic). One disadvantage of Isomalt is that due to it not being absorbed it remains in the intestinal tract longer and the non-absorbed carbohydrates create an osmotic effect that pulls water into the large intestine. When the non-absorbed carbohydrates reach the colon, normal bacteria metabolize them to gases and short-chain fatty acids which can lead to flatulence and loose stools.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1985 established a temporary acceptable daily intake (ADI) of 0-25 mg/kg until additional data from chronic toxicity studies was conduct. In 1987 JECFA reviewed the chronic toxicity study where isomalt was administered as 10% of the diet and established the ADI as "not specified" meaning there was no upper level for intake. It was acknowledged by JECFA that high doses of isomalt has a laxative effect in man but that the finding was common to all polyol (sugar alcohol) sweeteners and that this side effect should be taken into account when considering levels of use alone or in combination.

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:**

1. Sugar-free ACTIQ Project: results of a preclinical bioequivalence study. [IND 27,428, N444, Study no. RD/FC 03014], Volume 1, pp. 227.

**Studies not reviewed within this submission:** Not applicable.

**2.6.2 PHARMACOLOGY:** No new studies were submitted.

**2.6.3 PHARMACOLOGY TABULATED SUMMARY:** No new studies were submitted.

**2.6.4 PHARMACOKINETICS/TOXICOKINETICS:**

See results in the Toxicology section of the review.

**2.6.6 TOXICOLOGY - ACTIQ**

**2.6.6.1 Overall toxicology summary**

General toxicology: In local tissue irritation studies in the dog model, treatment with commercial ACTIQ lead to abrasions, while the formulations containing Isomalt did not lead to abrasions but lead to redness. Formulations chosen for the human bioequivalent studies were "B" which is a — isomalt/Fentanyl with a pH — and "C" which is a — ratio pH 6.6.

Genetic toxicology: No new studies were reviewed for fentanyl citrate.

Carcinogenicity: No new studies were reviewed for fentanyl citrate.  
Reproductive toxicology: No new studies were reviewed for fentanyl citrate.  
Special toxicology: No new studies were reviewed for fentanyl citrate.

**2.6.6.2 Single-dose toxicity:**

**Study title: Sugar-free ACTIQ Project: results of a preclinical bioequivalence study**

Key study findings:

- Mucosa abrasions were observed with the commercial ACTIQ product
- No abrasions or swelling, but redness was observed with the Isomalt 100/PEG 8000 formulations
- All formulations, except A, were found to be bioequivalent to the commercial ACTIQ
- Formulations B and C are being further developed by the Sponsor

Study no.: RD/FC 03014

Volume #, and page #: 1, pp. 227

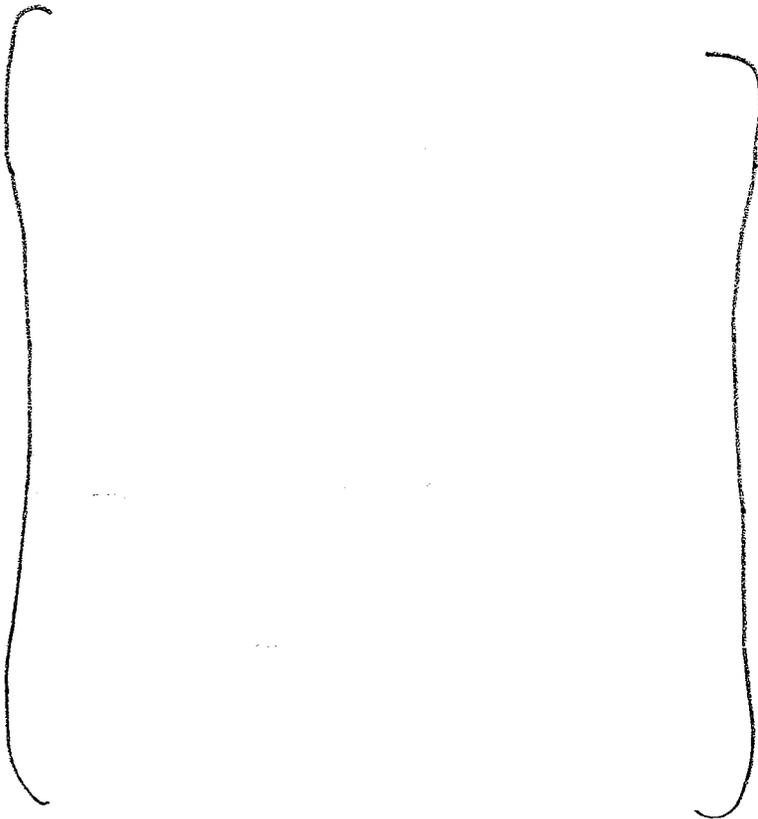
Conducting laboratory and location: Cephalon, Inc., Salt Lake City Operations

Date of study initiation: September 2003

GLP compliance/QA report: yes ( ) no (X)

Drug, lot #, and % purity: Certificate of Analysis was not provided.

Formulation	Ingredients	Lot No.	Dose ( $\mu$ g)	Target <sup>1</sup> pH	Batch size (kg)
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**2.6.6.4 Genetic toxicology**

No new studies were submitted for review.

**2.6.6.5 Carcinogenicity**

No new studies were submitted for review.

**2.6.6.6 Reproductive and developmental toxicology**

No new studies were submitted for review.

**2.6.6.7 Local tolerance**

No new studies were submitted for review.

**2.6.6.8 Special toxicology studies**

No new studies were submitted for review.

**2.6.6.9 Discussion and Conclusions****2.6.6.10 Tables and Figures:** Not applicable.

See results in the Toxicology section of the review.

**2.6.7 TOXICOLOGY TABULATED SUMMARY:** Not applicable.**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Commercial ACTIQ lead to abrasions, while the formulations containing Isomalt did not lead to abrasions but lead to redness. Formulations chosen for the human bioequivalent studies were "B" which is a  $\frac{1}{2}$  (Isomalt/fentanyl) at a pH  $\frac{1}{2}$  and "C" which is an  $\frac{1}{2}$  ratio at a pH  $\frac{1}{2}$ .

Following oral administration, Isomalt is minimally absorbed, distributed, and metabolized. It is significantly excreted unchanged in the feces. It was also not mutagenic in the Ames assay, carcinogenic in mice or rats, and did not cause reproductive toxicity in rats or rabbits at doses up to 10% in the diet.

The amount of Isomalt in each ACTIQ lozenge is  $\frac{1}{2}$  which is equivalent to  $\frac{1}{2}$  g if the lozenge is completely dissolved using a Q6H dosing regimen. Isomalt, alone or in combination with other sugar alcohols, is readily used in OTC 'sugar-free' products. The table below provides that estimated amount of isomalt or the sugar alcohols that are in the OTC products. The table indicates that the amounts of isomalt in OTC products, both as an individual unit dose and calculated using a dosing regimen of Q2H (up to 12-times a day ingestion) range from 1.8-39.12 g. The range of amounts where Isomalt exerts a laxative effect is 20-50 g in adults and 10-40 g in pediatric patients. The amount of Isomalt in the ACTIQ lozenge is within the range of OTC products and is 1-5 times below the laxative exerting amounts. Since opioids, such as fentanyl, are known to increase GI tone leading to a decrease in GI motility, the laxative effect may be beneficial in these patients and will likely not be a serious adverse effect.



Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay. Isomalt was not mutagenic in the *in vitro* Ames reverse mutation assay. 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. Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg i.v. and 160 mcg/kg subcutaneously. Reproduction studies in rats revealed a significant decrease in the pregnancy rates 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.

Isomalt did not affect fertility in rats when administered as 10% of the diet

### **Pregnancy - Category C**

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

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

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

Pregnant female New Zealand White rabbits were treated with fentanyl \_\_\_\_\_ a intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 5-times the human dose of 1600 mcg every 6 hours on a mg/m<sup>2</sup> basis).

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

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

No 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. It is not known whether Isomalt is excreted in human breast milk.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Suzanne Thornton-Jones  
3/11/05 03:45:35 PM  
PHARMACOLOGIST

R. Daniel Mellon  
3/11/05 04:13:57 PM  
PHARMACOLOGIST  
I concur.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

---

NDA: 20-747                      Submission Date: 11/19/04  
Submission Type; Code: SCF-019  
Brand/Code Name: ACTIQ®  
Generic Name: Oral Transmucosal Fentanyl Citrate  
Primary Reviewer: David Lee, Ph.D.  
Secondary Reviewer: Suresh Doddapaneni, Ph.D.  
OCPB Division: Division of Pharmaceutical Evaluation 2  
ORM Division: Division of Anesthetic, Critical Care and Addiction  
Drug Products  
Applicant: Cephalon, Inc  
Relevant IND(s): 27,428  
Cross References: NA  
Formulation; Strength(s): Solid, \_\_\_\_\_  
200, 400, 600, 800, 1200, 1600 µg  
Approved Indication: 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  
Approved Dosage                      ACTIQ should be individually titrated to a dose that  
Regimen:                              provides adequate analgesia and minimizes side  
   effects. The ACTIQ unit should be consumed over  
   a 15-minute period. 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). 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.

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## 1 Executive Summary

Cephalon has submitted a prior approval chemistry supplement. This supplement proposes a ‘sugar- free’ formulation [the proposed drug product is presented in the same six (6) dosage strengths (200, 400, 600, 800, 1200 and 1600 µg) as the current formulation] for ACTIQ® to replace the currently approved \_\_\_\_\_ formulation, i.e., with ‘sugar,’ described in S-008 (submitted August 8, 2001, approved on February 19, 2003, and since July of 2003 the formulation described has been the commercially available formulation). The Applicant stated that the new formulation may reduce the risk of dental decay and it removes the need to caution diabetic patients that marketed ACTIQ contains approximately 2 grams of sugar per unit.

The Applicant stated that the fentanyl citrate drug substance and the overall drug product remained the same for the proposed formulation (refer to CMC Review of this Supplement S-019).

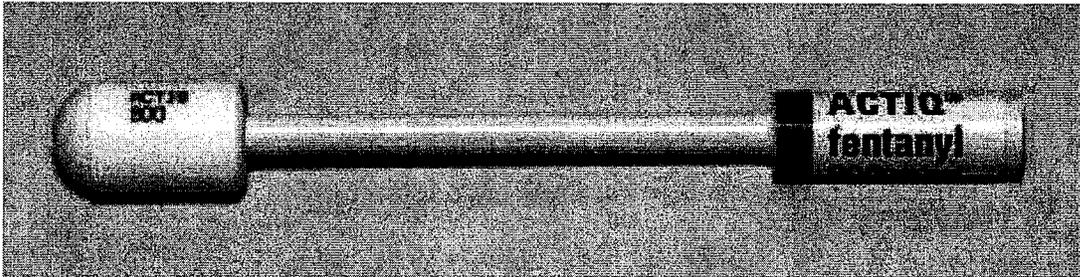


No serious adverse events occurred. Thirty (100%) subjects in this study experienced a total of 575 treatment-emergent adverse events. A total of 523 (91%) adverse events were mild in intensity, and 52 (9%) adverse events were moderate. Vital-signs related adverse events were commonly noted in this study, and 28 of the 30 subjects had vital signs results outside of the pre-specified ranges; however, all vital signs parameters were within normal limits at the end of the study and no marked mean vital signs changes from baseline were noted. Mean pulse oximetry (SpO<sub>2</sub>) measurements observed across all 3 treatments at baseline and post baseline were within normal limits with no marked mean changes from baseline noted.

## 2 QBR

### 2.1 General Attributes of the Drug and Drug Product

The proposed formulation of ACTIQ (oral transmucosal fentanyl citrate, OTFC) retains the same function and overall product description as the current approved formulation. ACTIQ provides a means to deliver fentanyl across the mucosal membranes of the buccal cavity for the purpose of attaining rapid onset of analgesia.



The image above (approximately twice actual size) shows the three main components of an ACTIQ bulk unit: the cap, the handle (or holder) and the handle tag.

#### 2.1.1 What are the treatments and subjects used in the bioequivalence study?

A total of 30 healthy subjects (15 men and 15 women) were enrolled in the bioequivalence study drug. Two sugar-free test formulations of oral transmucosal fentanyl citrate (800 µg), test formulation A (treatment B) and test formulation B (treatment C), separated by washout periods of 7 days (lot numbers C4CFC031 and C4CFC030, respectively) were included. For study drug administration training purposes, placebo units (lot number C4LFC005) were administered the night before the first administration of study drug.

### 2.2 General Clinical Pharmacology

**2.2.1 Are there any safety issues with the proposed 'sugar-free' formulation?**

Toxicology data were provided in the

Applicant stated that isomalt (dextrates replacement in the 'sugar-free' formulation) is widely used in the U.S. as an excipient in over-the-counter medications, and the Agency recognizes isomalt as a non-carcinogenic carbohydrate sweetener in foods that does not promote dental caries [see 21 CFR 101.80(c) (2) (ii) (A)].

**2.2.2 Are the sugar-free and approved formulations bioequivalent?**

Statistical analysis of the pharmacokinetic data demonstrated that ACTIQ and sugar-free test formulation A (treatment B) are bioequivalent on the basis of Cmax and AUC.

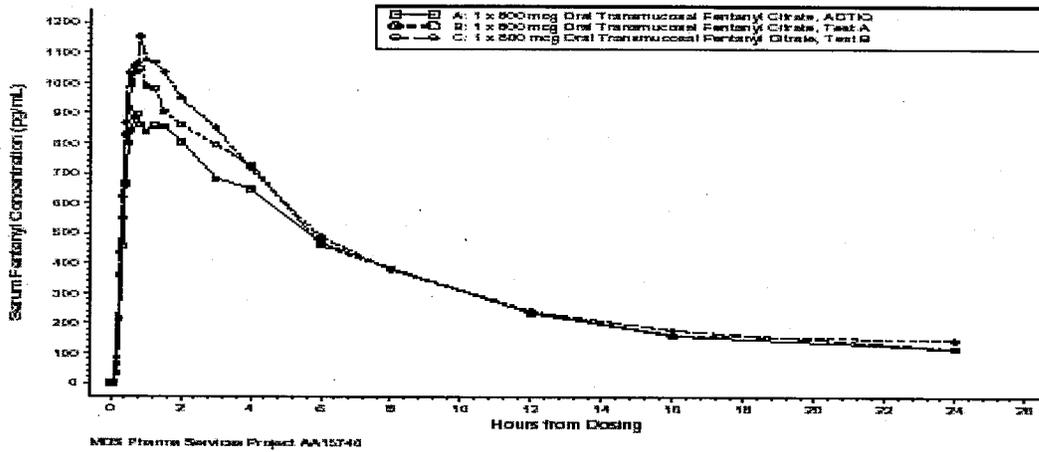
Pharmacokinetic parameters	Serum fentanyl		90% confidence interval	% mean ratio
	Formulation A Treatment B (N=26)	ACTIQ Treatment A (N=28)		
Cmax (pg/mL)	1278±396	1123 ± 319	-	-
AUC0-24 (pg hr/mL)	8525.7±2509.2	7915.0±3071.1	-	-
tmax (hr)	0.828 ±0.533	1.42±1.70	-	-
AUC0-t (pg hr/mL)	8504.4±2538.8	7872.2±3120.7	-	-
ln(Cmax)	7.106±0.3177	6.982±0.3049	102.47 - 124.0	112.7
ln[AUC0-24]	9.008±0.3006	8.901±0.4028	106.64 - 121.9	114.0
ln[AUC0-t]	9.004±0.3076	8.891±0.4158	107.24 - 122.8	114.8

Treatment B=1 x 800 mcg oral transmucosal fentanyl citrate (sugar-free test formulation A).

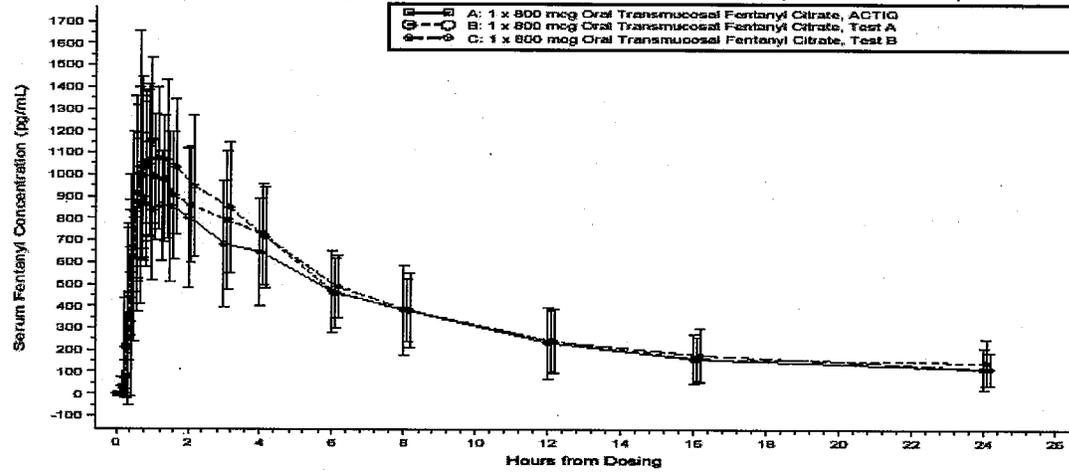
Treatment A=1 x 800 mcg oral transmucosal fentanyl citrate (ACTIQ [reference]).

No serious adverse events occurred. Thirty (100%) subjects in this study experienced a total of 575 treatment-emergent adverse events. A total of 523 (91%) adverse events were mild in intensity, and 52 (9%) adverse events were moderate. Vital-signs related adverse events were commonly noted in this study, and 28 of the 30 subjects had vital signs results outside of the pre-specified ranges; however, all vital signs parameters were within normal limits at the end of the study and no marked mean vital signs changes from baseline were noted. Mean pulse oximetry (SpO2) measurements observed across all 3 treatments at baseline and post baseline were within normal limits with no marked mean changes from baseline noted.

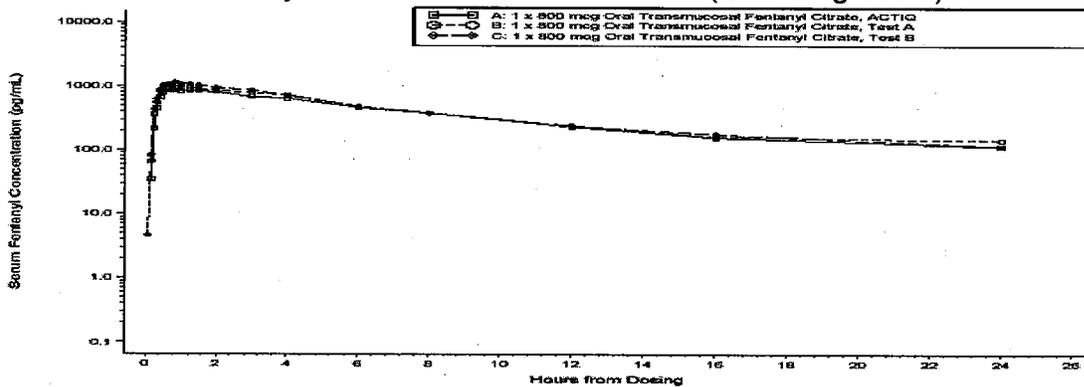
Mean Serum Fentanyl Concentrations Versus Time (Linear Scale)



Mean (SD) Serum Fentanyl Concentrations Versus Time (Linear Scale)



Mean Serum Fentanyl Concentrations Versus Time (Semi-Log Scale)



Division of Scientific Investigations audited this study and recommended that data from this study be accepted for review as the audit did not reveal any deficiencies (see Review dated 3/7/05 by Amalia Himaya, CSO).

**2.3 Intrinsic Factors – Not applicable**

**2.4 Extrinsic Factors – Not applicable**

**2.5 General Biopharmaceutics**

**2.5.1 How is the 'sugar-free' formulation different from approved drug product?**

The "sugar" excipient in the current product, dextrans, will be replaced by isomalt and PEG 8000. Isomalt is a \_\_\_\_\_ grade of the disaccharide polyol (sugar alcohol) isomalt derived from sucrose. Isomalt is a compendial material in the Ph Eur. Incorporation of isomalt in the USP/NF is in progress. The overall formulation is provided below:

Ingredient	Function	Standard or grade	Dosage unit formula by strength (fentanyl base)							
			All ingredients in mg							
			200 µg	400 µg	600 µg	800 µg	1200 µg	1600 µg		

The different strengths of sugar-free ACTIQ are proportionally similar as can be seen from the table above. Fentanyl comprises less than \_\_\_\_\_ of the total weight of \_\_\_\_\_ grams. As such a biowaiver can be granted for the 200, 400, 600, 1200, and 1600 µg based on the results from 800 µg strength in the bioequivalence study C8278/1020/BE/US. Comparative dissolution data for all strengths are provided below.

### 2.5.2 What does the dissolution data look like?

Test / Method	Dissolution / TM-00144						
Specification	NOTE: The specifications below are based on test results for registration batches at release and on stability. t=5 minutes:						
	S1n=6, Q = 10%, No individual value is outside of Q ± 5% S2n=6, Average of 6 units (S1+ S2) falls within the range stated in Stage 1 and no individual is more than 5% outside the stated range. S3n=12, Average of 24 units (S1+ S2+ S3) falls within the range stated in Stage 1, no individual is more than 10% outside the stated range, and no more than 2 units are more than 5% outside the stated range. t=5 minutes:						
	S1n=6, Q = 10% Each unit is not less than Q - 5% S2n=6, Average of 6 units (S1+ S2) is equal to or greater than Q, and no unit is less than Q - 5% S3n=12, Average of 24 units (S1+ S2+ S3) is equal to or greater than Q, and no more than 2 units are less than Q - 5%, and no unit is less than Q - 5%						
	Percent fentanyl released						
Batch #/strength	Minutes	5	10	15	20	30	40
C4CFC004 800µg n=36	High	41.6	77.1	96.1	102.0	105.5	109.0
	<b>Avg</b>	<b>26.2</b>	<b>46.1</b>	<b>61.9</b>	<b>74.6</b>	<b>89.6</b>	<b>100.6</b>
	Low	17.9	29.6	39.2	47.6	67.6	96.9
C4CFC009 200µg n=12	High	40.6	80.2	100.4	105.8	108.5	109.3
	<b>Avg</b>	<b>29.4</b>	<b>53.7</b>	<b>75.5</b>	<b>91.0</b>	<b>105.1</b>	<b>106.1</b>
	Low	27.0	48.2	64.6	80.2	102.2	101.0
C4CFC010 200µg n=36	High	36.4	69.4	89.5	97.3	103.9	104.5
	<b>Avg</b>	<b>28.1</b>	<b>53.3</b>	<b>74.6</b>	<b>89.6</b>	<b>98.7</b>	<b>99.1</b>
	Low	10.1	35.0	56.2	74.3	93.9	94.0
C4CFC011 200µg n=12	High	34.7	70.9	90.3	94.5	101.2	101.7
	<b>Avg</b>	<b>26.5</b>	<b>48.6</b>	<b>68.9</b>	<b>84.6</b>	<b>97.2</b>	<b>99.1</b>
	Low	21.9	36.6	53.2	64.9	87.2	94.1
C4CFC013 600µg n=36	High	39.4	73.7	91.4	99.5	104.3	105.0
	<b>Avg</b>	<b>30.9</b>	<b>55.1</b>	<b>74.0</b>	<b>88.0</b>	<b>99.0</b>	<b>100.5</b>
	Low	25.5	42.9	58.4	70.8	94.2	95.2
C4CFC014 1200µg n=36	High	40.0	69.8	93.0	106.7	111.6	111.6
	<b>Avg</b>	<b>29.9</b>	<b>53.3</b>	<b>73.0</b>	<b>88.0</b>	<b>101.7</b>	<b>104.1</b>
	Low	21.6	38.5	53.0	67.4	90.1	96.5
C4CFC015 1600µg n=12	High	38.9	73.2	92.6	97.5	98.7	106.6
	<b>Avg</b>	<b>27.1</b>	<b>47.9</b>	<b>64.8</b>	<b>77.8</b>	<b>92.5</b>	<b>99.2</b>
	Low	19.5	31.7	40.5	54.7	77.1	97.0
C4CFC016 1600µg n=12	High	33.4	63.1	86.4	97.7	103.5	103.4
	<b>Avg</b>	<b>29.4</b>	<b>55.3</b>	<b>78.1</b>	<b>93.6</b>	<b>100.9</b>	<b>101.1</b>
	Low	26.4	48.2	71.1	88.6	98.9	99.2
C4CFC017 1600µg n=12	High	38.2	69.6	88.5	98.1	103.2	104.1
	<b>Avg</b>	<b>26.1</b>	<b>45.1</b>	<b>61.7</b>	<b>73.5</b>	<b>89.5</b>	<b>101.3</b>
	Low	20.2	32.3	41.4	48.4	66.8	98.3
C4CFC042 400µg n=12	High	34.3	68.6	91.2	99.9	103.8	104.6
	<b>Avg</b>	<b>29.7</b>	<b>55.9</b>	<b>78.1</b>	<b>94.0</b>	<b>100.6</b>	<b>100.8</b>
	Low	25.5	47.1	68.7	87.2	97.5	97.9
Range of averages	High	30.9	55.9	78.1	94.0	105.1	106.1
	Low	26.1	45.1	61.7	73.5	89.5	99.1

**2.5.3 What is the effect of formulation factors on in vitro dissolution and in vivo bioavailability?**

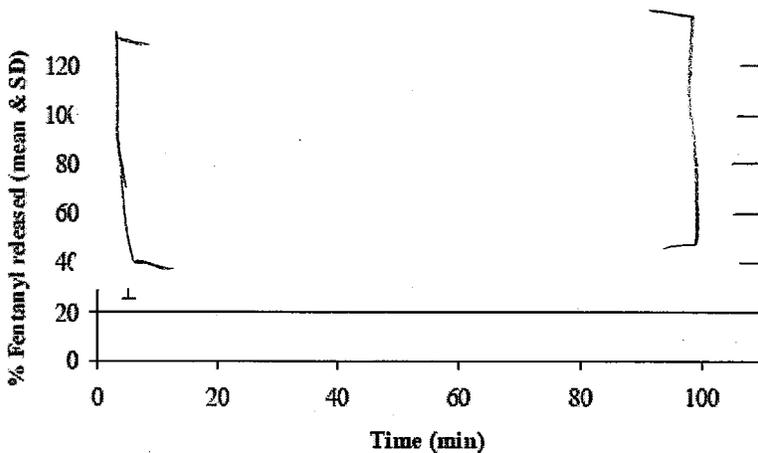
The patient controls the dissolution rate by actively sucking or rubbing the matrix unit against their buccal mucosa to promote erosion or surface dissolution of the dosage unit. Since the patient actively controls the rate of dissolution, in vitro dissolution does not predict in vivo bioavailability. However, the currently marketed product is bioequivalent to both the \_\_\_\_\_ and the \_\_\_\_\_ versions.

**Dissolution Profiles of 3 Types of Bioequivalent OTFC Products Tested Using TM 00062**

Type	No. of units and batches tested	Mean & (SD) % fentanyl released by time in minutes					
		5	10	20	30	40	100



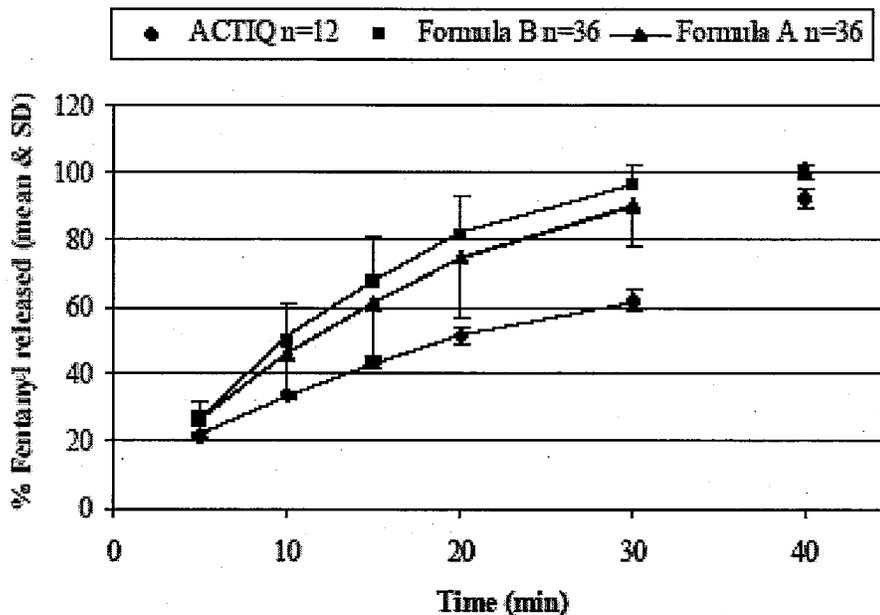
**Dissolution Profiles of 3 Bioequivalent OTFC Product Types Tested Using TM-00062 Developed for the Currently Approved ACTIQ Formulation**



With respect to formulations used in the BE study, it is noted that Formula A (isomalt/PEG 8000 \_\_\_\_\_) was bioequivalent to the currently approved ACTIQ product. These results further illustrate that the in vitro dissolution

characteristics of different OTFC formulations cannot be used to predict bioavailability.

Comparison of in vitro Dissolution Profiles for the 3 Biobatches Used in Bioequivalence Study C8278/1020/BE/US Using TM-00144 Developed for the Proposed ACTIQ Formulation



## 2.6 Analytical Section

2.6.1 Is fentanyl identified and measured in the serum in the bioequivalence studies? What bioanalytical methods are used to assess concentrations?

[ ]

2.6.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ ULOQ)? What is the accuracy, precision and selectivity at these limits? What is the sample stability under the conditions used

[ ]



### **3 Detailed Labeling Recommendations**

There are no changes recommended for the Clinical Pharmacology section of the label. See Appendix 4.1 for the Applicant's package insert proposal.

## **4 Appendices**

### **4.1 Proposed Package Insert with comments**

26 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-\_\_\_\_\_

## 4.2 Individual Study Review

Clinical Study Report C8278/1020/BE/US

Title of Study: An Open-Label, Randomized, Crossover Bioequivalence Study of ACTIQ® (800 Micrograms) and 2 Sugar-Free Test Formulations

[ ]

Study Period: 26 March 2004 to 12 April 2004 Phase of Development: 1

Primary Objective: To determine the bioequivalence of the reference:formulation A, and reference:formulation B, on the basis of natural log-transformed values for the area under the fentanyl serum concentration-time curve from time zero to 24 hours (AUC<sub>0-24</sub>) and maximum fentanyl serum concentration (C<sub>max</sub>).

Secondary Objectives:

- to determine and compare the early exposures (area under the fentanyl serum concentration-time curve from time zero to the median time of the maximum fentanyl serum concentration [t<sub>max</sub>] of the reference formulation [AUC<sub>0-tmax</sub>]) of reference:formulation A; and reference:formulation B;
- to determine and compare t<sub>max</sub> and area under the fentanyl serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC<sub>0-t</sub>) of the test and reference formulations;
- to assess safety by evaluating adverse events (comprising of withdrawals attributed to adverse events and serious adverse events including deaths), results of clinical laboratory tests, vital signs and saturated partial pressure of oxygen (SpO<sub>2</sub>) measurements, and oral mucosa and physical examinations
- to assess taste attributes by completing a questionnaire

Number of Subjects Planned (Analyzed): A total of 30 subjects (15 men and 15 women) were enrolled and received study drug. A total of 26 subjects (14 men and 12 women) completed the study. Data from 29 subjects were included in the pharmacokinetic analysis and statistical analysis of pharmacokinetics, and 30 subjects in the safety analysis. Bioequivalence was evaluated using data from all subjects who completed at least two treatment periods.

Diagnosis and Main Criteria for Inclusion: Written informed consent was obtained; the subject was from 19 to 50 years of age; the subject was in good health as determined by a medical and psychiatric history, medical examination, serum chemistry, hematology, urinalysis, and serology. Women must have been surgically sterile, 2 years postmenopausal, or, if of childbearing potential, must have been using a medically accepted method of birth control. No oral or cyclical contraceptives were allowed; the subject had a body mass index from 20 through

28 kg/m<sup>2</sup>; and the subject was willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period, and to return to the clinic for the follow-up evaluation as specified in the protocol.

**Main Criteria for Exclusion:** The subject had any clinically significant uncontrolled medical conditions (treated or untreated); the subject had a clinically significant deviation from normal in the physical examination; the subject was pregnant or a lactating woman (Any woman who became pregnant during the study was to be withdrawn from the study.); the subject tested positive for human immunodeficiency virus (HIV), hepatitis B surface antigen, or hepatitis C antibody; the subject had donated blood within 60 days or plasma within 7 days of the first administration of study drug; the subject had a hemoglobin value below 12 g/dL; the subject had used an investigational drug within 30 days before the screening visit; the subject had any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery); the subject had a known or suspected hypersensitivity to any compound present in the study drug; the subject had a history of, or current evidence of, abuse of any drug substance, including alcohol; the subject was currently using or had a history of tobacco or nicotine use within 6 months (180 days) before the first administration of study drug; and the subject had administered any medication, including over-the-counter medications, within 10 days before the first administration of study drug excluding the allowed contraceptives mentioned in the inclusion criteria.

**Study Drug Dose, Mode of Administration, Administration Rate, and Lot and Batch Number:**

**Investigational Product:** Two sugar-free test formulations of oral transmucosal fentanyl citrate (800 µg), test formulation A (treatment B) and test formulation B (treatment C), separated by washout periods of 7 days (lot numbers C4CFC031 and C4CFC030, respectively) were included.

**Placebo:** For study drug administration training purposes, placebo units (lot number C4LFC005) were administered the night before the first administration of study drug.

**Reference Therapy Dose, Mode of Administration, and Administration Rate:** Current commercially available ACTIQ (800 mcg) (treatment A) was administered transmucosally over 15 minutes with a washout period of 7 days (lot number: P52299).

**Duration of Treatment:** After enrolling, each subject was expected to participate in the study for approximately 16 days.

**Primary Efficacy Variables and Endpoints:** The primary variables were AUC<sub>0-24</sub> and C<sub>max</sub>.

Secondary Efficacy Variables and Endpoints: The secondary variables and endpoints were as follows: □AUC0-tmax.; □tmax; □AUC0-t; □vital signs, with the subject in recumbency, after each blood collection (within 30 minutes before study drug administration and after 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, and 90 minutes and after 2, 3, 4, 6, 8, 12, 16, and 24 hours): -systolic and diastolic blood pressure with an automated noninvasive blood pressure cuff; -pulse; -respiratory rate by manual counts; □SpO2 as measured by a pulse oximeter attached to the subject's finger or toe after each blood collection (immediately before study drug administration and after 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, and 90 minutes and after 2, 3, 4, 6, 8, 12, 16, and 24 hours); □oral mucosa exam by a licensed dentist immediately before and at 30 minutes and 12 hours after the commencement of the administration of the study drug; □clinical laboratory test results at study entry and exit (hematology, serum chemistry, and urinalysis); □complete physical examination at the screening and exit visits; □the frequency, intensity, and causality of adverse events throughout the study; □taste attribute questionnaire after each administration.

Statistical Considerations: Summary statistics including mean, standard deviation (SD), coefficient of variation (CV %), standard error of the mean (SEM), number of observations (N), minimum, maximum, and median were calculated by treatment. Mean and individual concentration-time plots were presented. Pharmacokinetic parameters were summarized by treatment using the previously listed descriptive statistics. Analyses of variance (ANOVA) were performed on the primary pharmacokinetic parameters Cmax and AUC0-24, and on the secondary parameters AUC0-tmax. and AUC0-t. Parameter values were log-transformed prior to analysis. The ANOVA model included sequence, formulation, and period as fixed effects, and subject nested within sequence as a random effect. The sequence effect was tested using subject nested within sequence as the error term. A 10% level of significance was used to test the sequence effect. Each ANOVA included calculation of least-squares means (LSMs), the difference between adjusted formulation means, and the standard error associated with this difference. Ratios of means were calculated by exponentiating the difference in the LSM (test/reference) of the natural-log.transformed pharmacokinetic parameters. Ratios of geometric means were expressed as a percentage relative to the reference formulation. Consistent with the 2 one-sided test for bioequivalence, 90% confidence intervals (CIs) for the difference between drug formulation LSMs were derived from the analyses on the natural-log.transformed pharmacokinetic parameters AUC0-24 and Cmax. The CIs were expressed as a percentage relative to the LSM for the reference formulation. Bioequivalence of the test and reference formulations was assumed if the 90% CIs for the Cmax and AUC0-24 mean ratios were completely contained in the interval 80% to 125%. The 90% CIs were also reported for the secondary parameters, AUC0-tmax. and AUC0-t; tmax was compared using the Wilcoxon Signed Rank Test and constructing 95% CIs using Walsh averages. Adverse events, clinical laboratory test results, vital signs and SpO2

measurements, and oral mucosa and physical examination findings were summarized by treatment group or treatment sequence group, as appropriate. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) were provided for actual values and changes from baseline, as appropriate. For categorical variables, frequency and percentage were provided.

Summary of Results:

Pharmacokinetics Results:

1. Statistical analysis of the pharmacokinetic data demonstrated that ACTIQ and sugar-free test formulation A (treatment B) are bioequivalent on the basis of C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-tmax</sub>.

- Median t<sub>max</sub> for test formulation A (treatment B) (0.674 hour [40.44 minutes]) was significantly earlier than the median t<sub>max</sub> for the reference formulation (treatment A) (0.841 hour [50.46 minutes]).
- Serum fentanyl pharmacokinetic parameters and statistical comparisons for sugar-free test formulation A (treatment B) and the reference formulation (ACTIQ [treatment A]) are summarized in the table below.

Pharmacokinetic parameters	Serum fentanyl		90% confidence interval	% mean ratio
	Formulation A Treatment B (N=26)	ACTIQ Treatment A (N=28)		
C <sub>max</sub> (pg/mL)	1278±396	1123 ± 319	-	-
AUC <sub>0-24</sub> (pg hr/mL)	8525.7±2509.2	7915.0±3071.1	-	-
t <sub>max</sub> (hr)	0.828 ±0.533	1.42±1.70	-	-
AUC <sub>0-tmax</sub> (pg hr/mL)	535.1±203.1	439.8±169.5	-	-
AUC <sub>0-t</sub> (pg hr/mL)	8504.4±2538.8	7872.2±3120.7	-	-
ln(C <sub>max</sub> )	7.106±0.3177	6.982±0.3049	102.47 - 124.0	112.7
ln[AUC <sub>0-24</sub> ]	9.008±0.3006	8.901±0.4028	106.64 - 121.9	114.0
ln[AUC <sub>0-tmax</sub> ]	6.210±0.3949	6.003±0.4378	110.24 - 134.3	121.7
ln[AUC <sub>0-t</sub> ]	9.004±0.3076	8.891±0.4158	107.24 - 122.8	114.8

Treatment B=1 x 800 mcg oral transmucosal fentanyl citrate (sugar-free test formulation A).

Treatment A=1 x 800 mcg oral transmucosal fentanyl citrate (ACTIQ [reference]).

2. Statistical analysis of the pharmacokinetic data demonstrated that sugar-free test formulation B (treatment C) and the reference formulation (ACTIQ [treatment A]) are not bioequivalent.

- The median t<sub>max</sub> for test formulation B (treatment C) was 0.833 hour (49.98 minutes) and was not significantly different from that of the reference formulation (treatment A [ACTIQ]).
- Serum fentanyl pharmacokinetic parameters and statistical comparisons for sugar-free test formulation B (treatments C) and the reference formulation (ACTIQ [treatment A]) are summarized in the table below.

Pharmacokinetic parameters	Serum fentanyl		90% confidence interval	% mean ratio
	Formulation B Treatment C (N=27)	ACTIQ Treatment A (N=28)		
C <sub>max</sub> (pg/mL)	1389±523	1123±319	-	-
AUC <sub>0-24</sub> (pg hr/mL)	8787.7±2961.8	7915.0±3071.1	-	-
t <sub>max</sub> (hr)	1.15±0.875	1.42±1.70	-	-
AUC <sub>0-t<sub>max</sub></sub> (pg hr/mL)	555.0± 220.3	439.8±169.5	-	-
AUC <sub>0-t</sub> (pg hr/mL)	8747.1±3003.3	7872.2±3120.7	-	-
ln(C <sub>max</sub> )	7.184±0.3211	6.982±0.3049	112.03 - 135.6	123.3
ln[AUC <sub>0-24</sub> ]	9.029±0.3247	8.901±0.4028	107.89 - 123.3	115.4
ln[AUC <sub>0-t<sub>max</sub></sub> ]	6.248±0.3864	6.003±0.4378	119.82 - 146.3	132.4
ln[AUC <sub>0-t</sub> ]	9.022±0.3327	8.891±0.4158	108.15 - 123.9	115.8

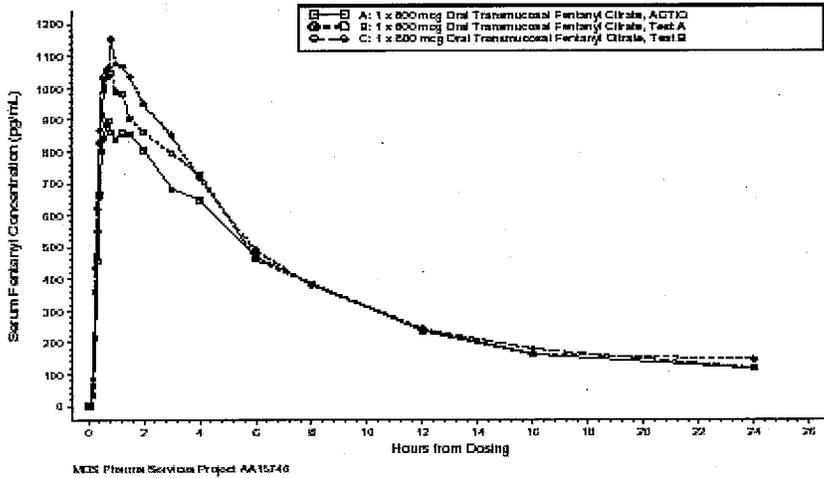
N=26 for AUC<sub>0-t<sub>max</sub></sub> for treatment C.

Treatment C=1 x 800 mcg oral transmucosal fentanyl citrate (sugar-free test formulation B).

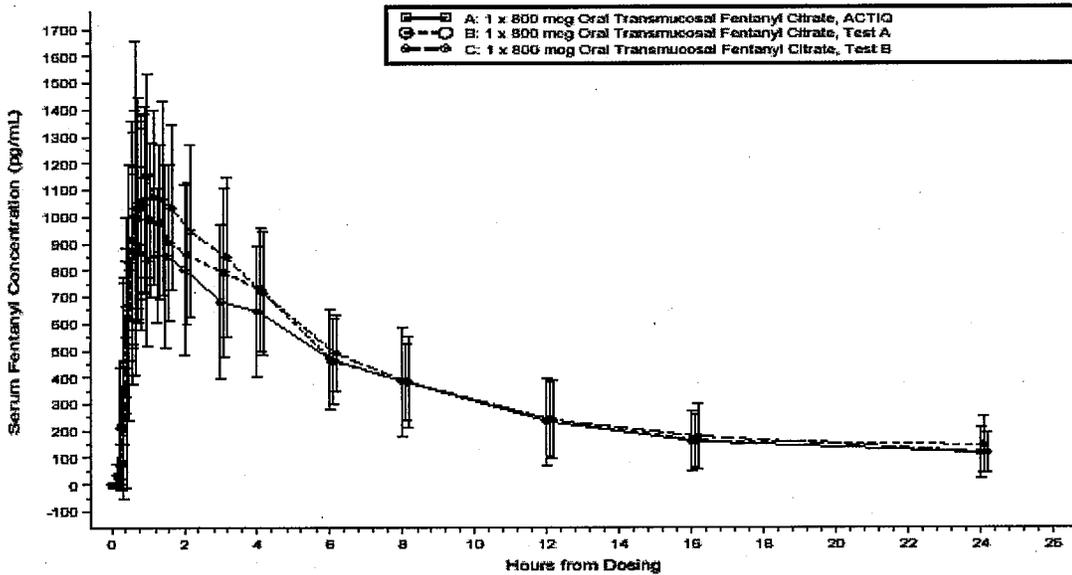
Treatment A=1 x 800 mcg oral transmucosal fentanyl citrate (ACTIQ [reference]).

### 3. Figures

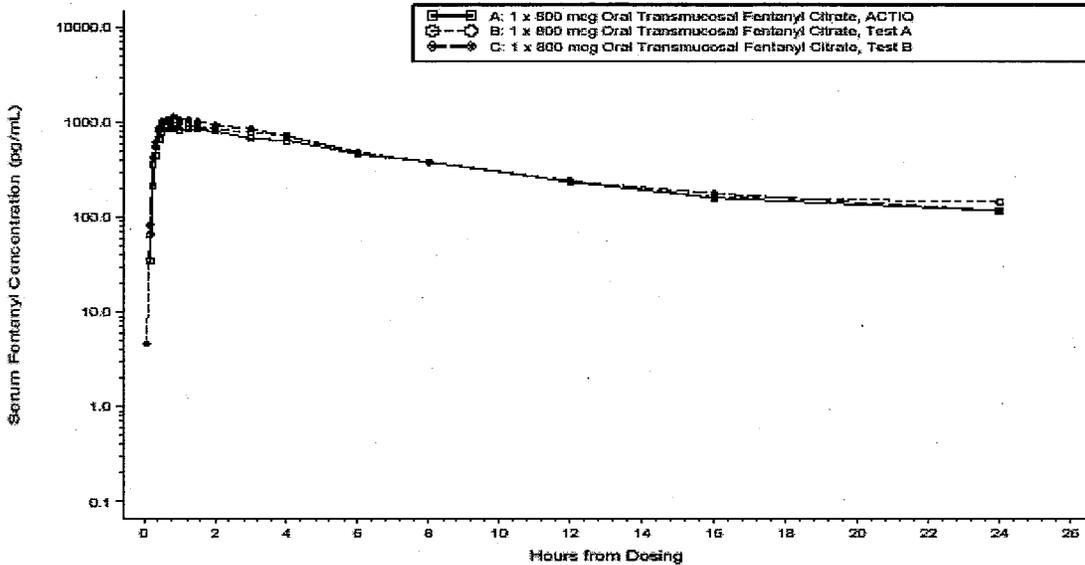
#### a. Mean Serum Fentanyl Concentrations Versus Time (Linear Scale)



b. Mean (SD) Serum Fentanyl Concentrations Versus Time (Linear Scale)



c. Mean Serum Fentanyl Concentrations Versus Time (Semi-Log Scale)



4. Safety Results:

- Thirty (100%) subjects in this study experienced a total of 575 treatment-emergent adverse events. A total of 523 (91%) adverse events were mild in intensity, and 52 (9%) adverse events were moderate.
- The principal investigator considered 539 (94%) adverse events to be possibly, probably, or definitely related to the study drug treatment.
- No serious adverse events occurred.
- Adverse events experienced in this study are known opioid effects of fentanyl citrate, have been observed in previous research studies, and included the following: respiratory depression, circulatory depression, hypotension, nausea, dizziness, somnolence, and vomiting. One subject was discontinued from the study due to the adverse event of hypotension, which is a known effect of the study drug.
- None of the adverse events in this study represented previously unsuspected important adverse events associated with ACTIQ treatment. No clear, treatment-related trends were observed in the clinical laboratory values, and the principal investigator did not consider any individual clinical laboratory abnormalities to be clinically meaningful.
- Vital-signs related adverse events were commonly noted in this study, and 28 of the 30 subjects had vital signs results outside of the prespecified ranges; however, all vital signs parameters were within normal limits at the

end of the study and no marked mean vital signs changes from baseline were noted.

- Mean SpO2 measurements observed across all 3 treatments at baseline and post baseline were within normal limits with no marked mean changes from baseline noted.
- Oral examination abnormalities following administration were generally mild, and the principal investigator did not consider any abnormal oral examination findings to be clinically meaningful.

### **Bioanalysis Final Report : Study AA15746-01**

For Protocol C8278/1020/BE/US : An Open- Label, Randomized, Crossover Bioequivalence Study of ACTIQ ( 800 Micrograms) and 2 Sugar- Free Test Formulations

LC- MS/ MS Method for the Determination of Fentanyl in Human Serum Study: AA15746- 01

#### **INTRODUCTION**

\_\_\_\_\_ has determined the concentrations of fentanyl in human serum using high performance liquid chromatography with mass spectrometric detection. Study samples were received as part of protocol number C8278/1020/BE/US, entitled, " An Open-Label, Randomized, Crossover Bioequivalence Study of ACTIQ (800 Micrograms) and 2 Sugar-Free Test Formulations," \_\_\_\_\_ study AA15746-01. Table 1 provides a listing of all batches and their respective analysis dates. This report provides the results and supporting documentation from the analysis of study samples as well as standard curve and quality control sample data.

#### **EXPERIMENTAL**

##### **Method and Materials**

##### **Analytical Method**

The analytical method was developed at \_\_\_\_\_

### Biological Matrix

Human serum was purchased from \_\_\_\_\_ Human serum, free of significant interference, was used to prepare calibration standard and quality control (QC) samples.

### Stock Solutions

Stock solutions were stored at a nominal temperature of -20 C.

### Calibration Curve Standards and Quality Control Samples

A set of eight non-zero calibration standards ranging from \_\_\_\_\_ pg/mL, and QC samples at three different concentrations: 150 pg/mL, 1500 pg/mL, and 3750 pg/mL were prepared and subsequently stored at a nominal temperature of -20°C. Calibration standards and QC samples were prepared on 02 Apr 2004.

### Sample Storage and Stability

Study samples were stored from sample collection to the end of sample analysis at a nominal temperature of -20°C for a duration not exceeding 28 days.

### Table 2: Stability Summary

#### Stability Summary



## RESULTS

1. All samples for a given subject were analyzed together in a single batch except when samples had to be reassayed. A batch, at a minimum, consisted of a set of calibration standards (consisting of a standard blank, a standard zero, and 1 replicate of least 8 different non-zero standards) and replicate low, medium, and high concentration quality control samples (QCs) were included to reflect at least 5% of the number of unknown samples (minimum n=2).
2. Batch Acceptance Criteria

Standards are rejected if they are greater than 15% (all standards but the LLOQ) or \_\_\_\_\_ (LLOQ only) of the nominal concentration. At least 75% of the non-zero standards are within the respective acceptance criterion. At least two-thirds of the low, medium, and high QCs, including at least 50% at each concentration level, are valid data points and are within 15% of the nominal concentration.

3. Quality Control Sample Analyses (Between-batch Precision and Accuracy)  
 Between-batch precision (%CV) and accuracy (%Bias) results for QC samples prepared at low, medium, and high QC concentrations. Precision was less than or equal to \_\_\_\_\_, accuracy ranged from \_\_\_\_\_.

4. Calibration Standard Concentrations  
 Accuracy (%Bias) ranged from \_\_\_\_\_.

5. Standard Curve Parameters  
 The coefficient of determination (R-squared) was 0.9904 or better.

6. Study Sample Concentrations  
 Study samples, if any, with no significant peak at the mass transition and retention time of fentanyl, or with peak area ratios below that of the LLOQ standard, are reported as being BLQ (< \_\_\_\_\_, ("Below the Limit of Quantitation").

**4.3 Consult Review (including Pharmacometric Reivews) – Not applicable.**

**4.4 Cover Sheet and OCPB Filing/Review Form**

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	20-747		Brand Name	ACTIQ
OCPB Division (I, II, III)	II		Generic Name	Fentanyl citrate
Medical Division	HFD-170		Drug Class	Opioid
OCPB Reviewer	David Lee		Indication(s)	For pain
OCPB Team Leader	Suresh Doddapaneni		Dosage Form	_____
			Dosing Regimen	single dose
Date of Submission	11/19/04		Route of Administration	Oral transmucosal
Estimated Due Date of OCPB Review	-		Sponsor	Cephalon, Inc
Medical Division Due Date	3/8/05		Priority Classification	
PDUFA Due Date				
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			

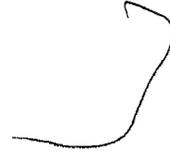
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2	2	
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				

Total Number of Studies		3	2	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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this page is the manifestation of the electronic signature.**  
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/s/

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David Lee  
3/17/05 10:12:39 AM  
BIOPHARMACEUTICS

A handwritten signature consisting of a large, stylized letter 'C' with a small arrowhead at the top right.A handwritten signature consisting of a large, stylized letter 'S' with a small arrowhead at the top right.

Suresh Doddapaneni  
3/17/05 10:19:52 AM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**20-747 / S-019**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**Division of Anesthetic, Critical Care, and Addiction Drug Products**

**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 20-747/S-019

**Name of Drug:** Actiq (oral transmucosal fentanyl citrate)

**Sponsor:** Cephalon, Inc.

**Material Reviewed**

**Submission Date(s):** November 19, 2004 and January 31, 2005 (BL) is the most current version of the proposed labeling and is reviewed here.

**Receipt Date(s):** November 19, 2004 and February 1, 2005 (BL).

**Background and Summary Description:** This supplement was submitted as a Prior Approval Chemistry supplement and proposes a formulation change to a sugar-free formulation, to replace the sugar-based formulation currently on the market.

The sponsor has estimated that, if approved, the sugar-free formulation will be launched in late 2005, and will have some market overlap with the sugar-based product (for approximately 6-9 months) while the supply of the sugared product currently in the market place is used up. The labeling on the current (sugared) formulation will not be changed as the sugar-free labeling will not be applicable to it.

The package insert (PI), and patient package insert (PPI) were compared to the approved labeling for the PI and PPI for S-017, submitted on March 24, 2004, approved on September 24, 2004. The carton labeling was compared to that approved with S-008, which was acknowledged and retained on September 21, 2004 (approved on February 19, 2003.)

**Status Report**

**Reviews Completed:** Kim Compton, RPM, February 25, 2005

**Reviews Pending:**

Pending: Clinical Review by Elizabeth McNeil, M.D.; CMC Review by Jila Boal, Ph.D., Pharmacology/Toxicology Review by Suzanne Thornton-Jones, Ph.D.

**RPM Review**

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label.

In addition to the changes noted in the labeling, in order to differentiate the sugar-free from the sugared product, the sponsor has proposed adding a sticker reading "Sugar-Free Formulation" as an "eyebrow" to the carton labeling for a period of 6 months after first introduction of the sugar-free product onto the market. This is proposed in order to avoid confusion between the sugar-free and currently approved sugared formulation while some current formulation remains in the market place until it is used up. After this 6 month period, the eyebrow sticker will not be used on the product.

**HEADER:** No changes noted

**BOX WARNING:** No changes noted

**WARNING:** No changes noted

**DESCRIPTION:**

The words "~~is radiopaque and~~" have been removed from the last sentence of the 1<sup>st</sup> paragraph of this section.

The new excipients have replaced the old in the "**Inactive Ingredients**" subsection as follows:

~~Hydrated dextrates~~ Isomalt, polyethylene glycol, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, and edible glue (modified food starch and confectioner's sugar).

**CLINICAL PHARMACOLOGY AND PHARMACOKINETICS:**

A footnote to Table 1 has been added in the title:

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

\* Based on arterial blood samples.

**CLINICAL TRIALS:** No changes noted

**INDICATIONS AND USAGE:** No changes noted

**CONTRAINDICATIONS:** No changes noted

**WARNINGS:** No changes noted

**PRECAUTIONS:**

In the second paragraph of the "Information for Patients and Their Caregivers" subsection, the following changes are proposed:

~~Frequent consumption of sugar-containing products may increase the risk of dental decay (each Actiq unit contains 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may increase the risk of dental decay add to this risk. The previous ACTIQ formulations contained approximately 2 grams of sugar per unit. The current ACTIQ formulation contains ISOMALT, the dextrate replacement, and less than 0.05 grams of sugar per unit which may reduce the risk of tooth decay.~~

In the paragraph following the above paragraph, the following changes are proposed:

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

The paragraph that followed the above paragraph has been deleted:

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

#### **ADVERSE REACTIONS:**

The following changes are proposed to the 1<sup>st</sup> two paragraphs of the "Post-Marketing Experience" subsection:

~~The following adverse reactions have been identified during postapproval use of Actiq. Because adverse 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.~~

The following adverse reactions have been identified during postapproval use of the previous Actiq formulations:

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

**DRUG ABUSE AND DEPENDENCE:** No changes noted

**OVERDOSAGE:** No changes noted

**DOSAGE AND ADMINISTRATION:** No changes noted

**SAFETY AND HANDLING:** No changes noted

**DISPOSAL OF ACTIQ:** No changes noted

**HOW SUPPLIED:**

New NDC numbers have been designated for the product as follows:

<u>Dosage Strength (fentanyl base)</u>	<u>Carton/Blister Package Color</u>	<u>NDC Number</u>
200 mcg	Gray	NDC 63459-502522-30
400 mcg	Blue	NDC 63459-504524-30
600 mcg	Orange	NDC 63459-506526-30
800 mcg	Purple	NDC 63459-508528-30
1200 mcg	Green	NDC 63459-512532-30
1600 mcg	Burgundy	NDC 63459-516536-30

**Patient Leaflet**

Under “What to expect from Actiq”, in the first sentence under bullet #4, the following changes have been proposed:

~~Frequent use of products that contain sugar may increase the risk of dental cavities or tooth decay (each Actiq unit contains about ½ teaspoon of sugar.)~~ The occurrence of dry mouth associated with the use of opioid medications may add to this the risk of dental cavities or tooth decay (ACTIQ contains the opioid medication fentanyl). You should consult your dentist to ensure appropriate dental care while using ACTIQ.

Bullet # 5 has been deleted:

~~Diabetic patients should inform their physician that they are taking Actiq, which contains two grams of sugar per unit (approximately ½ teaspoon).~~

**Carton Labeling**

**Side Panel 1**

The following changes have been proposed:

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

**Side Panel 2**

New patent numbers and an updated copyright date have been added.

Top Panel

The proposed “temporary (6 months) eyebrow” sticker that reads “Sugar-Free Formulation” is to be affixed at the top of the top panel. Currently the panel is blank except for the following statement at the bottom of the top panel:

**IMPORTANT:**

**Safe use of this product requires that the patient and/or caregiver read the enclosed patient leaflet for important warnings and directions.**

**RECOMMENDATIONS**

The labeling will be reviewed by the team as part of preparation for the action on this supplement. The represented disciplines will provide input on appropriate changes to update the label as needed.

Supervisory Comment/Concurrence/Parinda Jani: 3-2-05

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/s/

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Kimberly Compton  
3/4/05 06:25:09 PM  
CSO

Concurred by CPMS, Parinda Jani on 3-2-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 17, 2005

FROM: Nilufer M. Tampal, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 20-747/S-019,  
ACTIQ<sup>®</sup> (Oral Transmucosal Fentanyl Citrate)  
Lozenges, Sponsored by Cephalon Inc.

TO: Bob Rappaport, M.D., Director, Division of  
Anesthetics, Critical Care and Addiction Drug  
Products (HFD-170)

At the request of HFD-170, the Division of Scientific Investigations conducted audit of the following bioequivalence study:

Study C8278/1020/BE/US: An Open-Label, Randomized, Crossover Bioequivalence Study of ACTIQ<sup>®</sup> (800µg) and T \_\_\_\_\_  
\_\_\_\_\_ Formulations Sponsored by Cephalon Inc.

The clinical and analytical portions of Study C8278/1020/BE/US were conducted at \_\_\_\_\_

Following the inspection at \_\_\_\_\_ (2/10-15/05), Form 483 was issued. Our evaluation of the significant finding is as follows:

[ ]

The firm's pre-study stability experiment did not mimic the conditions of sample analysis. However, QC samples

processed with the subject samples and interspersed throughout the study runs performed acceptably; no instability was noted. While the firm's pre-study validation experiment should have demonstrated the stability of fentanyl in extracted samples under actual storage conditions, this observation does not impact the study outcome.

**Conclusion:**

Following our evaluation of the inspectional finding, DSI recommends that the data from Study 8278/1020/BE/US be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Nilufer M. Tampal, Ph.D.

**Final Classification:**

VAI - ~~\_\_\_\_\_~~

cc:

HFD-45/RF

HFD-48/Tampal (2)/Himaya/CF

HFD-170/Compton

HFD-870/Doddapaneni

HFR-SW3515/Mueller

Draft: NMT 02/17/05

Edit: JAO 2/28/05

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FACTS ID: 609227

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/s/

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Amalia Himaya

3/7/05 01:58:18 PM

CSO

Paper copy signed by Dr. Viswanathan on 3/7/05 and  
available upon request.