
From: Morrison, Jacqueline [/O=CEPHALON/OU=US01 ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=JMORRISO]
Sent: 1/20/2006 12:19:04 PM
To: Sales PCS Northwest [salespcsnorthwest@cephalon.com]
Subject: Actiq slide kit
Attachments: ActiqApproved Promo Slide Kit_11_04_04.ppt

Hi Everyone,

Attached is the comprehensive slide deck for MEP's, it has about 95 slides. Remember your speakers have the option of using either slide kit; they just need to give a 20 minute presentation before the Q & A. You may want to save this for your records.

Regards,

Jackie Morrison
Area Manager- Pacific Northwest
Pain Care Division
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ACTIQ[®] C-II
(oral transmucosal fentanyl citrate)

ACT 227

Black Box Warning

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

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Overview of Chronic Cancer Pain

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Components of Chronic Cancer Pain

- Persistent pain
 - Pain lasting ≥ 12 hours per day controlled by long-acting opioid therapy
- Breakthrough cancer pain (BTCP)
 - Transitory flare of moderate-to-severe pain occurring against a background of persistent pain otherwise controlled by chronic opioid therapy

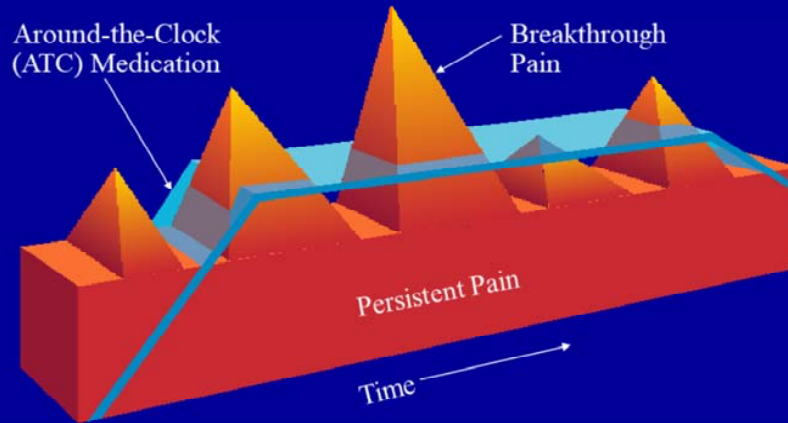
Portenoy RK, Hagen NA. *Pain*. 1990;41:273-281.

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Persistent Pain—When cancer pain becomes moderate to severe, it is often present most of the time, day and night. Portenoy and Hagen defined persistent or baseline pain as pain reported by the patient as the average pain intensity experienced for 12 or more hours during the 24 hours prior to the interview.¹ Persistent pain may also be referred to as constant or basal pain. Persistent pain is managed with medications dosed on a regular schedule around the clock (ATC), with the goal of alleviating pain until patients report no more than a mild to moderate “daily average” of pain.

Breakthrough Pain—Chronic pain is not static, and even when persistent pain is well controlled, flares of pain occur, typically rising to moderate or severe intensity. Breakthrough pain can specifically be defined as a transient flare in pain, rising to moderate-to-severe intensity, occurring in conjunction with a persistent pain that is controlled and of no more than mild or moderate intensity.¹ Breakthrough pain should be distinguished from uncontrolled pain, in which even the persistent pain is escalating and severe.

Components of Moderate-to-Severe Chronic Cancer Pain



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There are 2 components of chronic cancer pain; persistent cancer pain and breakthrough cancer pain (BTCP). Long-acting opioids are commonly used to manage the persistent pain. However, these medications are not indicated for the management of BTCP.

Cancer Pain Assessment

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Keys to Appropriate Pain Assessment

- Awareness of common pain syndromes
- Complete initial pain assessment
- Utilize appropriate assessment tools
 - Patient self-report
 - Easily administered pain rating scales
 - Documentation forms available to all clinicians
- Assess pain at regular intervals
- Assess both components of chronic pain – persistent pain and breakthrough pain

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Proper assessment of cancer pain involves several steps. Clinicians must ask patients about pain and provide an initial assessment that includes a medical history, information about pain intensity and characteristics, a physical examination, a psychosocial examination, and where appropriate, a diagnostic evaluation of signs and symptoms associated with common pain syndromes. Healthcare professionals should use the patient self-report as the primary source of assessment, should document pain intensity and relief via at least 1 easily administered scale, and should make pain intensity records available to all clinicians involved in treatment. Patients and their families should be trained in the proper use of pain assessment tools for home use as well. After the comprehensive initial pain assessment, pain should be assessed at regular intervals, after the development of new pain or following modification of the treatment plan. Physicians should be aware of common pain syndromes.²

Pain Assessment Tools: Temporal Nature of Pain

- Intensity of persistent and breakthrough pain
- Number of breakthrough pain episodes/day
- Timing of breakthrough pain relative to ATC dosing interval
- Location of breakthrough pain relative to persistent pain
- Efficacy of analgesia for both persistent pain and breakthrough pain
 - Onset
 - Peak
 - Duration

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Pain is a dynamic symptom, with fluctuations that may relate to activity, stress, analgesic dosing, or other variables. Temporal factors that may aid clinical decisions include onset and duration of pain, intensity, frequency of exacerbations, intensity of breakthrough pain relative to persistent pain, timing of breakthrough pain relative to ATC dosing intervals, and the efficacy of analgesia (or nonpharmacologic therapy) in controlling either persistent or breakthrough pain. It may also be helpful to ask patients about the location of breakthrough pain relative to persistent pain, particularly since cancer pain may be attributed to a variety of sources.

Understanding the temporal nature of pain is clinically relevant because patients with persistent cancer pain are typically treated with both ATC medication for persistent pain and breakthrough pain medication for exacerbations of pain. Exacerbations of pain that coincide with the end of an ATC dosing interval often indicate a need for increased ATC dosage or shortened ATC dosing intervals. Breakthrough pain that occurs with disturbing frequency (eg, more than 4 times daily) or that cannot be treated rapidly and effectively with breakthrough pain medication may also mandate an increased ATC dosage. Breakthrough pain is appropriately treated with a short-acting, rapid onset breakthrough pain medication. Effective treatment of breakthrough pain may lead to decreased dosage of ATC medication.

Characteristics of Breakthrough Cancer Pain

- Moderate-to-severe intensity
- Rapid onset (peaks in <3 minutes in 43% of patients)
- Often unpredictable, strikes without warning
- Relatively short duration
 - On average, lasts for up to 30 minutes
- Frequency: 1-4 episodes per day

Portenoy RK, Hagen NA. *Pain*. 1990;41:273-281.

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Breakthrough cancer pain is a common clinical phenomenon. Historically, BTCP has been assessed as a secondary outcome measure in studies evaluating the efficacy of an ATC medication.^{3,4,5} This approach focused on end-of-dose failure and not on incident pain or idiopathic/spontaneous pain. In a study of 22 hospice patients, up to 86% of the patients surveyed had episodes of breakthrough pain.⁶

In their first publication prospectively examining breakthrough pain, Portenoy and Hagen surveyed 63 cancer patients who were referred to an inpatient cancer pain service—notably a group with numerous pain problems. Transient flares of severe or excruciating pain were reported by 41 patients (64%).¹

Portenoy later examined another inpatient group of 164 cancer patients. The prevalence values were similar to those of the first study: 84 of 164 (51.2%) patients reported breakthrough pain.⁷

Portenoy also reported preliminary results from a multinational study conducted by the International Association for the Study of Pain (IASP) Task Force. This group evaluated 1095 patients, of whom 64.8% reported breakthrough pain. Breakthrough pain in this study was defined as transitory flares of pain above baseline levels, as identified by observer-rated measures.⁸

Based on the results from 1 survey, the onset of BTCP is often sudden, reaches maximum severity within 3 minutes, and lasts for a median duration of 30 minutes.¹

Types of Breakthrough Pain

- Incident/activity related
 - Movement
 - Coughing/sneezing
 - Touch
- Idiopathic/spontaneous
- End-of-dose failure

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The concept of breakthrough pain has been relatively ill defined until recently. In 1990, Portenoy and Hagen published a landmark survey that has allowed investigators to use standard definitions of both breakthrough and persistent pain. Using these standardized definitions it is now possible to compare different studies defining the characteristics of breakthrough pain, and more recently to design studies aimed specifically at treating breakthrough pain.

Pain is an unstable phenomenon that may vary with numerous factors, including disease progression, activity level, specific movements, or stress level. Most patients experience numerous peaks and valleys of pain daily. Optimal pain management requires an understanding of the variable nature of pain. Medications should be dosed consistently with this variability.

There are 3 types of BTCP – spontaneous, incident, and end-of-dose failure. The etiology of BTCP may be related to a tumor, its treatment, and other diseases or causes unrelated to cancer.

Breakthrough pain is best managed with specific medications with attributes that match the characteristics of breakthrough pain. Breakthrough pain does not necessarily mean that ATC analgesia has failed. A more detailed discussion on the approach to managing breakthrough pain and persistent pain follows later in this module.

Pharmacologic Management of Chronic Cancer Pain

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Treatment of Chronic Cancer Pain – Goals of Effective Pharmacologic Management

- Select/prescribe the appropriate drug
 - Appropriate dose
 - Appropriate route of administration
 - Appropriate dosing interval
- Control persistent pain
- Recognize and treat breakthrough pain
- Titrate doses aggressively
- Anticipate, prevent, and manage side effects
- Use appropriate adjuvant drugs when indicated
- Assess treatment response at regular intervals

Adapted from Levy MH. *N Engl J Med.* 1996;335:1124-1132.

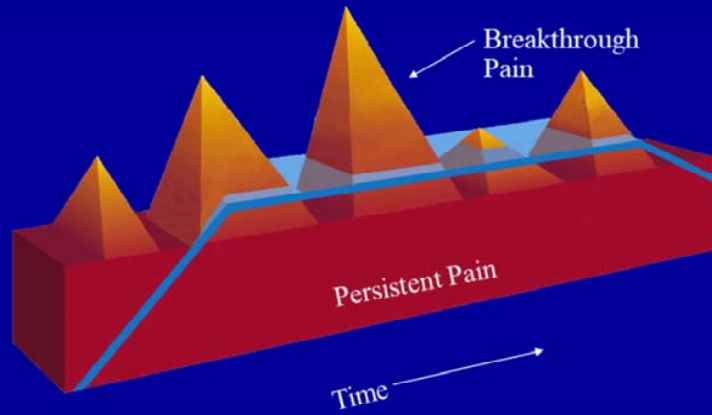
ACT 227

Millions of patients experience chronic cancer pain that should be adequately treated. Once pain has been properly assessed, appropriate pharmacologic management of cancer pain requires choosing an appropriate agent and route of analgesic administration, titration of dosing and manipulation of timing the doses, management of side effects, and use of adjuvant agents, when necessary. Empiric pain therapy should be started while awaiting the results of more definitive diagnostic studies or a response to antineoplastic therapy. General principles of pain therapy, in brief, are:

- Analgesic agents should be selected based on the severity of pain
- Less invasive routes should be used in preference to more invasive routes
- Opioid doses should be titrated to achieve maximal analgesia with acceptable side effects
- Drugs should be prescribed to prevent persistent pain and relieve breakthrough pain
- Constipation should be treated prophylactically, and antiemetics and similar agents should be used when appropriate to limit analgesic side effects
- The use of adjuvant agents (NSAIDs, anticonvulsants, tricyclic antidepressants, and corticosteroids) may enhance analgesic effects, and such agents may be more useful than opioids in treating some types of pain, such as neuropathic pain
- Frequent pain assessment is a key feature to maximizing analgesia and minimizing side effects

These issues will be discussed in more detail later in this slide kit.

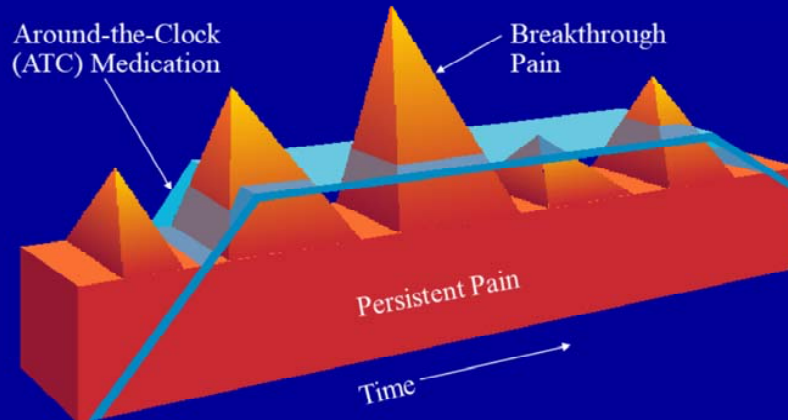
Components of Moderate-to-Severe Cancer Pain



ACT 227

There are 2 components of chronic cancer pain: persistent cancer pain and BTCP. Long-acting opioids are commonly used to manage the persistent pain. However, these medications are not indicated for the management of BTCP.

Around-the-Clock (ATC) Medication – Treating Persistent Pain



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Persistent pain—pain which lasts 12 or more hours per day — is 1 component of chronic cancer pain. Persistent pain is best treated with medications that are administered on an ATC basis to provide relatively constant blood levels. Opioid ATC dosing is usually achieved with an opioid that has prolonged absorption, such as controlled-release oral medications or transdermal medications. Dosing intervals are adjusted to ensure that blood concentrations do not fall significantly at the end of the dosing interval. The goal is to remain above the analgesic threshold and to cover the persistent pain constantly, without overmedicating.

Goals of Breakthrough Cancer Pain Medication

- Onset and duration of effect that closely match that of a BTCP episode
- Short duration of effect
- Manageable side effects
- Noninvasive
- Easy to use
- Cost effective

Portenoy RK, Hagen NA. *Pain*. 1990;41:273-281.

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The goal for breakthrough pain medication usage is to treat breakthrough pain rapidly and effectively, without overmedicating the patient.

Characteristics of breakthrough pain medications are:

- Onset and duration of effect that closely match that of a BTCP episode
- Short duration of effect
- Manageable side effects
- Noninvasive
- Easy to use
- Cost effective

ACTIQ® C-II

(oral transmucosal fentanyl citrate)

Indication

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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, and disposed of properly, and subsequent doses should be decreased.

Black Box Warning

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

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Route of Administration

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Oral Transmucosal System (OTS™) Drug Delivery Technology

ACTIQ uses OTS technology to deliver fentanyl



ACT 227

ACTIQ uses the oral transmucosal system (OTS™) delivery system for rapid non-invasive delivery of fentanyl and patient-controlled administration.

With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

Fentanyl Characteristics

- Potent opioid analgesic
- Highly lipophilic compound
- Slow gastrointestinal absorption following oral administration
- Rapid and extensive distribution into tissues, including central nervous system
- Elimination by hepatic metabolism (CYP3A4)
 - Terminal elimination half-life ($T_{1/2}$) ~7 hours
 - Pharmacologically inactive metabolites (eg, norfentanyl) are primarily excreted in the urine

American Hospital Formulary Service (AHFS), 2003.

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Oral transmucosal technology may be applicable to many drugs. The first drug to which the oral transmucosal technology has been applied is fentanyl citrate. It is a prime example of how oral transmucosal dosing affects drug absorption and bioavailability. Fentanyl has important pharmacokinetic properties that explain both its rapid onset of action and relatively short duration of effect in the OTS delivery platform.

Fentanyl was chosen in part because of its potency and lipophilicity, which are key attributes for agents delivered through the OTS.⁹ Fentanyl is a synthetic opioid with a potency much greater than that of morphine. Introduced into clinical practice in the 1960s, fentanyl has since been widely used intravenously for anesthesia. Fentanyl has been formulated for transdermal delivery and used as an analgesic in the treatment of chronic cancer pain. Fentanyl is lipid soluble, which allows it to pass rapidly via the transcellular route through the oral mucosa.

The lipophilic nature of fentanyl also allows it to be distributed widely and rapidly into tissues. When IV fentanyl was administered to normal volunteers at a dose of 15 $\mu\text{g}/\text{kg}$, the volume of distribution at steady state was much larger than the blood volume and was measured to be 287 ± 79 L. The peak blood level seen soon after an IV injection was followed by an initial rapidly falling blood level as fentanyl was rapidly redistributed in the tissues. This rapid fall during the redistribution phase explains fentanyl's short duration of effect after a bolus injection. Absorption of fentanyl following oral administration (swallowed) is very slow, approximately 1/3 of the swallowed dose enters the systemic circulation.

Fentanyl is metabolized by the liver, as are most metabolites, and eliminated in the urine. The primary metabolite is norfentanyl. Metabolites of fentanyl are pharmacologically inactive (in contrast with morphine) and do not accumulate and cause CNS excitation (in contrast with meperidine).¹⁰ Terminal elimination half-life for ACTIQ is 460 ± 313 minutes.¹¹ The terminal elimination explains the long tail seen after the rapid redistribution phase. Clearly the systemic effects of fentanyl are determined more by the rapid distribution phase than the relatively slow terminal elimination phase. Systemic effects may be shorter due to redistribution within tissues.¹⁰

Fentanyl: Routes of Administration

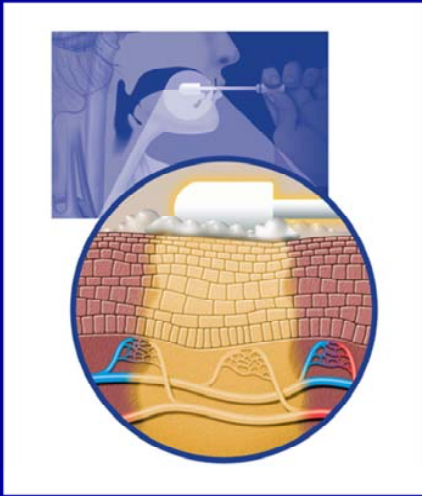
- Oral
- Parenteral
 - eg, intravenous, subcutaneous, epidural
- Transdermal
- Transmucosal

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Several routes of analgesic administration are currently utilized, including oral, transdermal, transmucosal, intraspinal, rectal, intravenous and subcutaneous, nasal, or intraventricular routes. Generally, less invasive routes are preferable to more invasive ones. The oral route is one of the most convenient, making it the route of choice when it can be used effectively. The oral route is not desirable in the setting of persistent nausea and vomiting, bowel obstruction, dysphagia, and malabsorption, and in patients who need rapid pain relief. Oral transmucosal administration may be a preferred route that offers convenience and more rapid onset of effect than some other oral medications.¹²

With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

Oral Transmucosal Route of Administration



Characteristics of oral mucosa provide an ideal route of administration

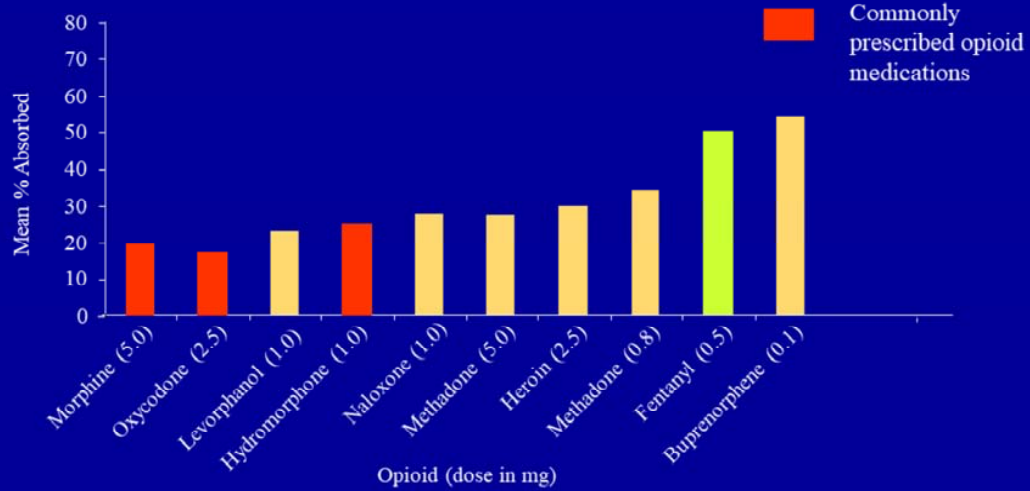
- Large surface area
- Uniform temperature
- High permeability
- Well vascularized
- Facilitates rapid absorption

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The oral transmucosal route of delivering drugs is desirable for several reasons. The oral cavity has a relatively uniform temperature and a large surface area. The oral mucosa is highly permeable — 20 times more permeable than the skin. Additionally, the oral mucosa is highly vascularized. Because of these characteristics, certain drugs are able to cross the oral mucosa and enter the bloodstream rapidly and directly, without hepatic and intestinal first-pass metabolism. Drug bioavailability is thus increased, and rapid onset of action is achieved without invasive methods.

Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of ACTIQ is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit of ACTIQ, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.¹³

Absorption of Opioids From Oral Mucosa



Adapted from Weinberg DS, et al. *Clin Pharm Ther*. 1988;44:337.

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Fentanyl was chosen for administration via the oral transmucosal route because it is very potent and readily absorbed from the oral cavity. Under conditions of controlled pH and minimal swallowing, sublingual absorption of 1 mL aliquots of various opioids was recorded in healthy volunteers over a 10-minute period, with 10 to 35 volunteers receiving each test drug.¹⁴ Drugs tested included morphine sulfate, oxycodone, levorphanol, hydromorphone, naloxone, methadone (2 concentrations), heroin, fentanyl, and buprenorphine. Overall, lipophilic drugs were better absorbed than hydrophilic drugs. Morphine was only 18% bioavailable. Methadone (34% absorbed), fentanyl (51%), and buprenorphine (55%) were absorbed to a significantly greater degree than morphine. Buprenorphine is only a partial mu-agonist and is not a good choice as a step 2 opioid. It also exhibits a depot effect when administered sublingually, and it has a prolonged duration of action. The pharmacokinetics of methadone (long plasma half-life) preclude its use as a breakthrough pain medication.

Lipid Solubility and CNS Equilibrium Times

	Morphine	Oxycodone	Fentanyl
Octanol/H ₂ O partition coefficient (lipid solubility)	1.4	0.7 ¹	813 ²
Keo T _{1/2} (time into CNS)	17 min ³	N/A	3-5 min ²

N/A=Not available.

1 - Oxycontin PI.

2 - ACTIQ PI.

3 - Kramer TH, d'Amours RH, Buettner C. *Clin Pharmacol Ther.* 1996;59:132.

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This slide reflects the lipid solubility of 3 agents: morphine, oxycodone, and fentanyl. The higher the octanol-to-water partition coefficient, the more lipid soluble it is and therefore the more readily it will cross the blood-brain barrier.

Optimal Conditions for Absorption Through Oral Mucosa

- Rate of consumption → relatively short (eg, 15 minutes)
- Saliva production → enough for dissolution
- Site of absorption → buccal mucosa (facilitates rapid absorption)
- pH of mouth → avoid low pH fluids (reduces ionization)
- Swallowing of drug → limited (minimizes GI absorption)

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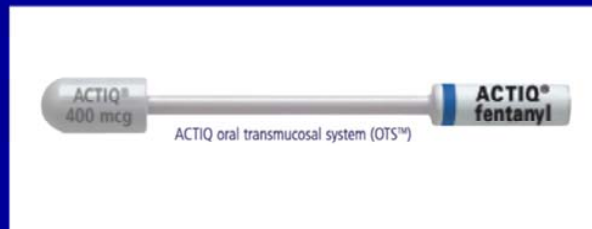
Several factors affect the absorption of drugs through the oral mucosa. First, the rate of consumption affects how quickly a drug travels across the oral mucosa.

Second, positioning of the matrix in the mouth affects absorption. Drug permeability is highest in the sublingual and buccal areas of the mouth and lowest in the gingiva and tongue.

Another factor affecting absorption is the pH of the mouth. Fentanyl is a weak base with a pKa of 8.4. When the pH in the mouth falls, more fentanyl is ionized (charged), limiting mucosal absorption. Low pH fluids such as coffee, cola, or citric fruit juices may reduce the local pH of the mouth and thereby decrease fentanyl absorption.

Attributes of ACTIQ

- Short consumption time (15 minutes)
- Rapid absorption across buccal mucosa* with slower GI absorption
- Noninvasive
- Convenient route of administration
- Favorable safety features (eg, product identification, removal of unit)



*Peak plasma concentration may vary if ACTIQ is chewed or swallowed.

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ACTIQ consists of a solid drug matrix attached to a handle. When the matrix dissolves in the patient's mouth, the drug becomes available for rapid absorption across the oral mucosa.

The ACTIQ handle allows patients to more easily twirl the unit in the mouth while applying it to the mucosal lining. It also allows patients to remove the product if they begin to experience side effects.

Another advantage of the ACTIQ unit is ease of administration. It is noninvasive and less complex for many patients than an IV set up or an electronic pump. The units are convenient to carry and can be administered readily as needed. No technical expertise or special equipment is required.

With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

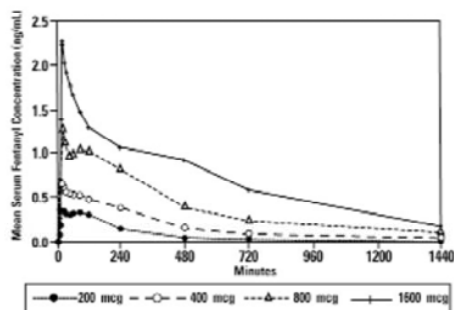
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Pharmacokinetics and Pharmacodynamics

ACT 227

Dose Proportionality Study – Fentanyl Concentration-Time Profile

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



Adapted from Streisand JB, et al. *Anesthesiology*. 1998;88(2):305-309.

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Dose proportionality among 4 of the available strengths of ACTIQ (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these 4 doses of ACTIQ are shown above. The curves for each strength level are similar in shape with increasing strength levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0 \rightarrow \infty}$ increased in a dose-dependent manner that is approximately proportional to the amount of ACTIQ administered.

Comparison of Different Formulations of Fentanyl – Parenteral, Oral Solution, Oral Transmucosal

- Study design: randomized, crossover, 3 treatment periods
- Study subjects: healthy male volunteers (n=12)
 - Mean weight: 76±5.4 kg
- Treatment periods:
 - Fentanyl dose – 15 µg/kg (~1200 mcg)
 - IV – continuous infusion at rate of 150 µg/min (~8 minutes)
 - Oral solution – ACTIQ unit dissolved in 10 mL sterile water and swallowed
 - Oral transmucosal – ACTIQ unit consumed over 15 minutes
- Pharmacokinetic parameters:
 - AUC, C_{max} and T_{max}

Streisand JB, et al. *Anesthesiology*. 1991;75:223-229.

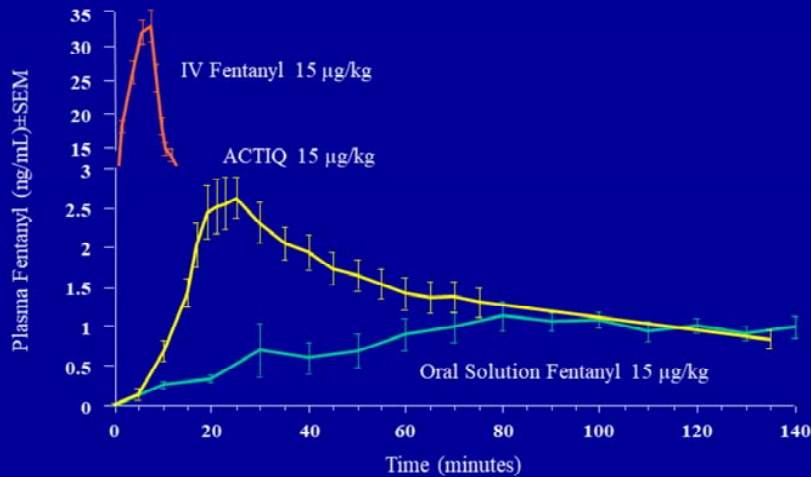
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Adult male volunteers were administered 15 µg/kg of fentanyl on 3 separate days, using 3 different routes of administration: IV, oral transmucosal, and oral solution.

When normal male volunteers swallowed a 15 µg/kg solution of fentanyl, the peak fentanyl level did not occur until approximately 1.5 hours after administration. The peak level after administration of the solution was lower than the peak seen following oral transmucosal fentanyl citrate (ACTIQ) administration (1.6 ng/mL for the oral solution compared to 2.7 ng/mL for ACTIQ). The overall bioavailability of swallowed fentanyl was 32%. The remaining 68% underwent first-pass metabolism in the liver or small intestine or was not absorbed.¹¹

When ACTIQ was given to healthy male volunteers, its pharmacokinetic curve looked similar to that of IV fentanyl, but changes in plasma levels occurred more gradually. Doses of 15 µg/kg were consumed within 15 minutes. The mean peak concentration (C_{max}) was 2.7 ng/mL, and that peak occurred 5-10 minutes after the ACTIQ unit had been completely consumed: T_{max} was 23 minutes.

Fentanyl Concentration-Time Profiles – Different Routes of Administration



Adapted from Streisand JB, et al. *Anesthesiology*. 1991;75:223-229.

ACT 227

Adult male volunteers were administered 15 µg/kg of fentanyl on 3 separate days, using 3 different routes of administration: IV, oral transmucosal, and oral solution. This graph compares the pharmacokinetics of the 3 delivery methods.¹¹

The peak level after IV administration occurred just after the IV infusion was stopped and reached a mean level of 16 ng/mL. The peak level with ACTIQ occurred at 23 minutes, which was 5-10 minutes after the ACTIQ unit was completely dissolved (mean administration time was 15 minutes). The mean peak level after ACTIQ administration was 2.9 ng/mL. The peak fentanyl level after swallowing the oral solution occurred much later (at an average of 101 minutes) and reached a mean level of 1.6 ng/mL.¹¹

Oral transmucosal delivery provides a peak fentanyl blood level significantly faster than a swallowed oral solution ($P=0.003$).¹¹ The pharmacokinetic profile of ACTIQ approximates that of IV fentanyl in terms of time to peak blood level.

With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

Fentanyl Pharmacokinetic Parameters – Different Routes of Administration

	IV	Oral Solution	ACTIQ
C_{\max} (ng/mL)	33.6±5.5	1.6±0.53	2.8±1.0
T_{\max} (min)	N/A	101.3±48.8	23.0±3.4
Bioavailability (F)	1.0	0.32±0.10	0.50±0.10
Percent (%)	100	32	50

C_{\max} = peak plasma concentration; T_{\max} = time to reach C_{\max} ; Bioavailability = The extent to which an administered drug becomes available to the systemic circulation (relative to IV).

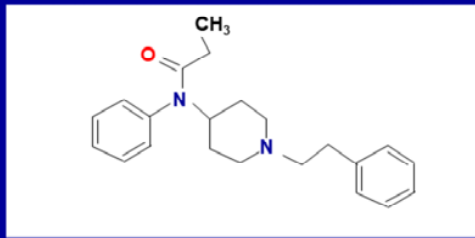
Adapted from Streisand JB, et al. *Anesthesiology* 1991;75:223-229.

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The data shown graphically on the previous slide are summarized in this table. ACTIQ attains maximum plasma levels almost twice as fast as those reached after administration of the oral solution. While maximum plasma levels are reached when the IV infusion is stopped, maximum plasma levels are obtained approximately 8 minutes after the 15-minute application of ACTIQ—23 minutes after ACTIQ was first administered. An oral solution, by contrast, takes 1 hour and 41 minutes to attain maximum plasma levels.¹¹

The bioavailability for IV administration was, by definition, 100%. The bioavailability for ACTIQ was 50% and for swallowed oral solution 32%. The decreased bioavailability for the oral solution is due in large part to first-pass metabolism in the liver and small bowel and may also be due in part to fentanyl that was never absorbed.¹¹

Fentanyl Metabolism



- Metabolized by liver and intestinal microsomes
- Catalyzed predominantly by P450 3A4
- Primary metabolite norfentanyl
 - Not pharmacologically active
 - Renal excretion

ACT 227

Kharasch demonstrated that human liver and intestinal microsomes catalyze fentanyl metabolism. The predominant route of biotransformation is to norfentanyl.¹⁵ Metabolism is catalyzed primarily by P450 3A4 in both liver and duodenal microsomes.

There are several clinical implications relevant to ACTIQ from these findings. Microsome enzyme activity may vary depending on interindividual variability in hepatic P450 3A4 expression and to drug interactions involving P450 3A4. There may be fast and slow metabolizers of fentanyl, and changes in other medications may also affect fentanyl metabolism.

Changes in the systemic metabolism should affect the terminal elimination phase of fentanyl. Changes in first-pass metabolism may affect the bioavailability of swallowed fentanyl.

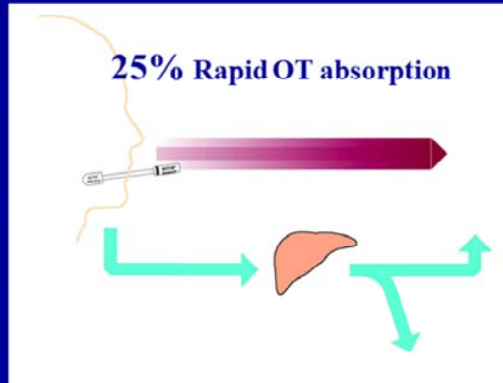
A large number of clinically important drugs act as substrates of the cytochrome P450 3A4 subfamily of metabolic enzymes. The cytochrome P450 3A4 isoform is possibly the most clinically important cytochrome P450 enzyme, comprising as much as 60% of the total cytochrome P450 content of the liver.¹⁶

The potential for metabolism-based drug-drug interactions associated with the use of ACTIQ involves both first-pass effects on swallowed fentanyl and clearance effects on fentanyl that has reached the systemic circulation. Inhibition of intestinal and hepatic P450 3A4 activity, for example, could potentially increase the bioavailability of swallowed fentanyl. The peak blood level with ACTIQ may not be affected because it is determined primarily by oral transmucosal absorption.

It is more difficult to predict the impact of drug-induced alterations in hepatic P450 3A4 on systemic clearance of fentanyl. Fentanyl is a high-extraction drug and should therefore be relatively insensitive to changes in hepatic intrinsic clearance caused by altered P450 3A4 activity.^{10,17} The effects of altered hepatic P450 3A4 activity on systemic fentanyl elimination, however, are unknown. By analogy, systemic clearance of intravenous sufentanil, also a high-extraction drug, is relatively unaffected by P450 3A4 inhibition by erythromycin.¹⁸ In contrast, systemic clearance of alfentanil, a low-extraction drug, is significantly diminished by erythromycin and other P450 3A4 inhibitors.^{19,20}

Total Fentanyl Bioavailability Following ACTIQ Administration Is 50%

After standardized consumption time of 15 minutes*



50% Total bioavailability

▶ 25% Rapid OT absorption

▶ 25% Slow GI absorption

▶ 50% Lost to metabolism

Adapted from Streisand JB, et al. *Anesthesiology* 1991;75:223-229.

*Peak plasma concentration may vary if ACTIQ is chewed or swallowed.

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Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of ACTIQ is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit of ACTIQ, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.¹³ Patients should not bite or chew ACTIQ.

Pharmacodynamics – Onset of Pain Relief

- Goal: onset of pain relief that is similar to onset of BTCP episode
 - Once in the bloodstream, fentanyl is rapidly distributed to the CNS (a process with a 3- to 5-minute half-life)
 - With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ but full relief may not be felt for up to 45 minutes after consuming an ACTIQ unit
 - Longer or shorter consumption times may produce less efficacy than reported in ACTIQ clinical trials

ACTIQ Package Insert. Rev. August 2004.

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For patients in moderate to severe pain, the time it takes to achieve meaningful pain relief becomes very important. Pharmacokinetic time profiles tell only part of the story. Once an opioid such as morphine or fentanyl enters the circulation, it must cross the blood-brain barrier before it reaches mu receptors in the CNS and exerts its analgesic effects.

With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

Patients should not bite or chew ACTIQ.

Pharmacodynamics – Duration of Pain Relief

- Goal: duration of pain relief would be similar to the duration of a breakthrough cancer pain episode
- In clinical trials
 - The duration of pain relief was measured for up to 1 hour following consumption of an ACTIQ unit
 - ACTIQ produced significantly ($P<0.0001$) more pain relief compared to placebo at all time points

Farrar JT, et al; *J Natl Cancer Institute*. 1998;90: 611-618. Lichtor JL, et al. *Anesth Analg*. 1999;89:732-738.

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In clinical trials, duration of pain relief was measured for up to 1 hour following consumption of an ACTIQ unit. In these studies, ACTIQ produced significantly ($P<0.0001$) more pain relief compared with placebo at 15, 30, 45, and 60 minutes following administration.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Clinical Trials
Dose Titration Studies

ACT 227

Study Design and Objectives

Study design: multicenter, randomized, double-blind

Primary objective

- To demonstrate that a titration process can be used to identify a dose of ACTIQ that safely and effectively treats breakthrough pain in cancer patients receiving around-the-clock (ATC) oral opioids or transdermal fentanyl to treat their persistent pain

Secondary objectives

- Assess dose response
- Establish ACTIQ dosing guidelines
- Define safety profile
- Compare ACTIQ with patients' usual breakthrough pain medications

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

ACT 227

The information in this section is based on 2 multicenter, dose titration studies of ACTIQ for the treatment of breakthrough pain in cancer patients. The first study evaluated ACTIQ in patients taking stable doses of oral morphine. The second evaluated ACTIQ in patients using ATC doses of transdermal fentanyl. The studies were conducted at 11 sites; 10 of these sites conducted both studies. Both studies have been reported in the medical literature.^{21,22}

Blinded Titration Studies in Patients on Oral and Transdermal ATC Opioids

Primary Objective

The primary objective of these studies was to demonstrate that a titration process can be used to identify a dose of ACTIQ that safely and effectively treats breakthrough pain in cancer patients receiving ATC oral opioids or transdermal fentanyl for their persistent pain.

Secondary Objective

A secondary objective was to compare ACTIQ with the usual supplemental pain medications used to treat breakthrough pain. These open-label comparisons allowed for an initial assessment of how well ACTIQ manages breakthrough pain compared with currently available supplemental medications.

Since elements of blinding were introduced during titration there was also the opportunity to assess dose response effects. For example, patients would be expected to get more pain relief at higher doses. And the successful dose for each patient should not depend on the dose at which they started the titration process. By examining the successful dose that was established for each patient, it is possible to see if this dose could have been predicted, for example by the dose of their ATC opioid. This type of analysis helps to establish ACTIQ dosing guidelines.

Eligible Patients

- Outpatients with cancer managing persistent pain with
 - Oral opioids, 60-1,000 mg/d morphine equivalent (n=65)
 - Transdermal fentanyl 50-300 mcg/hr (n=62)
- Experiencing 1-4 breakthrough pain episodes per day

ACT 227

Sixty-five patients managing their ATC pain with oral opioids entered the oral study. The mean morphine equivalent dose range for these patients was 60-1000 mg/d.

Transdermal Study

Sixty-two patients using transdermal fentanyl ATC entered the transdermal study. The mean dose was 50-100 mcg/hr.

Patients in both studies were experiencing 1-4 breakthrough pain episodes per day.

Study Design

Baseline Phase

Assess baseline performance of usual supplemental opioid for breakthrough pain



ACTIQ Phase

- ACTIQ titration to define successful dose (200 mcg-1600 mcg)*
- Assess performance of ACTIQ at successful dose

*Successful dose=1 dosage strength of ACTIQ could be used consistently for at least 2 consecutive days to treat BTCP without unacceptable side effects.

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

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These 2 studies used the same design which was comprised of 2 phases: a baseline phase and an ACTIQ phase. The ACTIQ phase was a double-blind, parallel group, dose titration phase which began after completion of the baseline phase. Before study start, the patients were taught how to consume an ACTIQ unit in 15 minutes. They were also taught how to properly complete study diaries.

Baseline Phase

The goal of the baseline phase was to evaluate the patient's breakthrough pain and the performance of their usual breakthrough pain medication.

Baseline data concerning the performance of the patient's usual breakthrough pain medication was collected on 2 consecutive days during a period of stable dosing. "Stable dosing" was defined as at least 3 consecutive days during which the scheduled opioid regimen yielded an average daily pain of moderate severity or less, tolerable opioid side effects, and 4 or fewer breakthrough pain episodes per day. Up to a month could be taken to stabilize the patient's opioid dose regimen if necessary. When patients had evaluated at least 1 breakthrough pain using their usual supplemental medication on 2 consecutive days they were considered to have completed the baseline phase of the study. The 2 days of baseline data formed a foundation against which subsequent comparisons were made once the patients were successfully titrated to a proper dose of ACTIQ for breakthrough pain.

ACTIQ Dose Titration Phase

The goal of the dose titration phase was to define a successful dose, whereby a single ACTIQ dosage unit provided adequate analgesia with acceptable side effects for 1 episode of breakthrough pain. The ACTIQ dose range was 200, 400, 600, 800, 1200, and 1600 mcg.

Assessment of Breakthrough Pain Treatment

End-of-Baseline and End-of-ACTIQ Phases

- 2-day observation
- After treatment, patients rated
 - Pain intensity (score 0 to 10)
0=No pain, 10=Pain as bad as you could imagine
 - Pain relief (score 0 to 4)
0=None, 1=Fair, 2=Good, 3=Very good, 4=Excellent
 - Medication performance (score 0 to 4)
0=None, 1=Fair, 2=Good, 3=Very good, 4=Excellent

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

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Throughout the study, patients used a diary to record pain intensity scores, pain relief scores, medication performance ratings, and adverse events. Patients evaluated pain intensity using a categorical rating scale that ranged from 0 (no pain) through 10 (pain as bad as you can imagine). Pain intensity differences were obtained by calculating the change in pain intensity at each time point compared with the 0 minute score. Patients rated pain relief using a 5-point scale ranging from 0 (none) to 4 (complete). The medication performance rating allowed patients to evaluate the performance of the study medication to treat their pain using a scale that ranged from 0 (poor) through 4 (excellent). Data collected during the 2-day baseline phase, while patients were using their usual supplemental medications, were compared with data from the 2 successful ACTIQ days.

ACTIQ Titration Procedure

- Investigator and patient blind to doses
- Start at 200 µg or 400 µg ACTIQ*
- Use up to 4 units/episode; treat up to 2 episodes/day
- Increase dosage if >1 unit needed per episode
- One-third of orders to increase dose ignored
- Titrate ACTIQ dose until 1 unit is effective for 2 consecutive days

*The package insert recommends a starting dose of 200 mcg.

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

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All patients who entered the dose titration phase were randomly assigned to begin treatment with either a 200 mcg or a 400 mcg ACTIQ unit. To ensure safety, patients in the transdermal study using less than 100 mcg/h transdermal fentanyl were always assigned to start with the 200 mcg ACTIQ. Only 1 dosage strength was administered at a time by an unblinded dispensing pharmacist. All units were identical in appearance (ie, not marked with dosage strength) and thus, both the patient and the investigator were blind to the starting dose.

Each day, up to 2 episodes of breakthrough pain could be selected for ACTIQ treatment. The usual supplemental pain medication was used to treat all other breakthrough pains on these study days. When the patients experienced an episode of breakthrough pain, they self-administered a complete ACTIQ unit. Patients were instructed to wait 15 minutes after finishing an ACTIQ unit. If adequate pain relief was not achieved they could take another unit. Up to 4 ACTIQ units could be taken for each episode of breakthrough pain (1 unit every 30 minutes). The patients were also instructed to wait 2 hours before treating a subsequent episode of breakthrough pain with ACTIQ. If additional pain relief was needed, the patients were encouraged to use their usual supplemental pain medication.

The decision to titrate or maintain the dose for another day was made following a daily telephone assessment that evaluated response to the ACTIQ, including the number of units consumed and a global evaluation of analgesia and side effects. Simple guidelines were developed to encourage consistency in the investigators' judgments concerning dose titration. Dosage strength was increased or decreased by a single step to the next available strength.

In order to create a stronger blind, orders to increase the dosage were randomly ignored 1/3 of the time by an unblinded dispensing pharmacist, according to a sponsor-supplied randomization schedule. Neither the patient nor the investigator was aware of the actual dose the patient received during the dose titration process.

The titration process continued until a single dose of ACTIQ was found that provided adequate relief of the target pain on 2 consecutive days.

A secondary objective of the study was to compare the performance of the usual breakthrough pain medication with the performance of ACTIQ after titration to an adequate dose of ACTIQ. For each breakthrough pain episode studied, pain intensity scores were obtained prior to use of breakthrough pain medication (usual supplemental medication during the baseline phase and ACTIQ during the ACTIQ phase). Pain intensity and pain reduction were reported at 15, 30, and 60 minutes following treatment. If a second dose of ACTIQ was needed to manage the pain, outcome data were collected at 15 minutes only. At the end of each day, patients provided a global evaluation of the performance of usual supplemental pain medication or ACTIQ. Side effects were also recorded.

Pain Pathophysiology

	Persistent Pain		Breakthrough Pain	
	Oral	Transdermal	Oral	Transdermal
Nociceptive - somatic	29 (45%)	35 (57%)	28 (43%)	34 (55%)
Nociceptive - visceral	14 (22%)	17 (27%)	15 (23%)	18 (29%)
Neuropathic	22 (34%)	10 (16%)	22 (34%)	10 (16%)

Note: Target breakthrough pain and persistent pain usually had the same pathophysiology.

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file. Cephalon, Inc.

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The specific characteristics of cancer pain may influence the outcome of therapy in analgesic studies. One of these characteristics is the pain pathophysiology. The vast majority of cancer patients have some identifiable pain pathophysiology, either nociceptive (related to ongoing activation of pain-sensitive primary afferent neurons) or neuropathic (related to an injury of neural tissues). Clinical experience and limited data from analgesic studies suggest that pain resulting from a neuropathic mechanism is less responsive to opioids than pain resulting from other mechanisms.⁵ There is also evidence, however, that pain pathophysiology cannot predict a patient's response to opioids.^{5,23}

The predominant pain pathophysiology for each patient was recorded at the beginning of the study. In nearly all cases, the patient's predominant persistent and breakthrough pain were of the same pathophysiology, suggesting that the patient's breakthrough pain was most likely an acute exacerbation of the persistent pain.

Oral Study

Forty-three patients (67%) had pain that was characterized as nociceptive: 29 patients (45%) had nociceptive-somatic pain, and 14 patients (22%) had nociceptive-visceral pain. Twenty-two patients (34%) had pain that was characterized as neuropathic.

Transdermal Study

Fifty-two patients (84%) had pain that was characterized as nociceptive: 35 patients (57%) had nociceptive-somatic pain, and 17 patients (27%) had nociceptive-visceral pain. Ten patients (16%) had pain that was characterized as neuropathic.

Patient Completion Status

	Oral (n=65)	Transdermal (n=62)
Found a successful dose of ACTIQ	48 (74%)	47 (76%)
Withdrew due to an adverse event	8 (12%)*	6 (10%)†
Not successful at 1600 mcg	5 (8%)	4 (6%)
Other withdrawal	4 (6%)‡	5 (8%)§

* 4/8 ACTIQ related.

† 3/6 ACTIQ related.

‡ Noncompliance (n=2), vacation, unable to consume first unit, inadequate pain relief.

§ Breakthrough pain ceased, scheduled for chemotherapy, incomplete pain relief, change in ATC dose.

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Oral Study

Sixty-five patients enrolled in the study. The majority of these patients (74%) titrated to a successful dose in the range offered in the study (200 mcg-1600 mcg).

Five patients (8%) were unable to control their breakthrough pain using the maximum dose offered in the study (1600 mcg).

Twelve patients (18%) withdrew from the study. Of the 12 withdrawals, 8 patients (12%) withdrew due to an adverse event. Four of these patients experienced adverse events that were considered by the investigators to be at least possibly related to ACTIQ. Adverse events in patients who withdrew were typical opioid-related events such as nausea, dizziness, and itching.

Four patients (6%) withdrew during the titration phase for reasons other than adverse events. These included cessation of breakthrough pain, chemotherapy, change in the fixed schedule drug, and inadequate pain relief.

Transdermal Study

Sixty-two patients enrolled in the study. The majority of these patients (76%) titrated to a successful dose in the range offered in the study (200 mcg-1600 mcg).

Four patients (6%) were unable to control their breakthrough pain using the maximum dose offered in the study, 1600 mcg.

Eleven patients (18%) withdrew from the study. Of the 11 withdrawals, 6 patients (10%) withdrew due to an adverse event. Three of these patients experienced adverse events that were considered by the investigators to be at least possibly related to ACTIQ. Adverse events in patients who withdrew were typical opioid-related events such as nausea, dizziness, and itching.

Five patients (8%) withdrew during the titration phase for reasons other than adverse events. These included noncompliance with study procedures, inadequate pain relief, inability to consume first unit of ACTIQ, and vacation.

Adverse Events

The most common adverse events (AEs):

	Oral [*]	Transdermal [†]
Somnolence	18 (28%)	11 (18%)
Dizziness	9 (14%)	6 (10%)
Nausea	5 (8%)	7 (11%)
Vomiting	2 (3%)	3 (5%)

^{*}Four patients withdrew with drug-related AEs: somnolence, dizziness, hallucination, body numbness, dry mouth, headache, nausea, vomiting.

[†]Three patients withdrew with drug-related AEs: shortness of breath, chest pains, disorientation, unsteady gait, weakness, dizziness, blurred vision, flushing, nausea.

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

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The adverse events associated with ACTIQ were typical opioid-related events. On the days that any ACTIQ was taken, adverse events that occurred with a frequency of >5% and were considered by the investigator to be possibly, probably, or almost certainly associated with the study drug. The events were comprised of somnolence (28%), dizziness (14%), nausea (8%), and headache (5%) in the oral study and somnolence (18%), nausea (11%), dizziness (10%), and vomiting (5%) in the transdermal study. These events, when experienced by a patient, were generally mild and often disappeared with continued exposure to ACTIQ.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

Summary –Dose-Titration Studies

- 75% of patients found a dose of ACTIQ that could successfully* treat their breakthrough pain
 - Regardless of pain pathophysiology, patients titrated to the same mean dose of 600 mcg
 - No difference in efficacy was noted in patients randomized to start on either 200 mcg or 400 mcg
 - The optimal dose of ACTIQ was determined by titration and cannot be predicted by the ATC dose
 - The most common side effects (somnolence, nausea, vomiting, and dizziness) were typical of opioids

*A successful dose of ACTIQ was defined as a dosage strength where 1 unit of ACTIQ could be used consistently for at least 2 consecutive days to treat breakthrough cancer pain without unacceptable side effects.

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Data on file, Cephalon, Inc.

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Study Results

The conclusions for these dose titration studies are as follows:

- 75% of patients found a dose of ACTIQ that could successfully* treat their breakthrough pain
- Regardless of pain pathophysiology, patients titrated to the same mean dose of 600 mcg
- No difference in efficacy was noted in patients randomized to start on either 200 mcg or 400 mcg
- The optimal dose of ACTIQ was determined by titration and cannot be predicted by the ATC dose
- The most common side effects (somnolence, nausea, vomiting, and dizziness) were typical side effects of opioids

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

*A successful dose of ACTIQ was defined as a dosage strength where 1 unit of ACTIQ could be used consistently for at least 2 consecutive days to treat BTCP without unacceptable side effects.

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Clinical Trials
Placebo-Controlled Study

ACT 227

Study Design and Objectives

Study design

- Multicenter, randomized, double-blind, placebo-controlled, crossover trial

Primary objective

- To evaluate the effectiveness of ACTIQ vs placebo in relieving breakthrough pain in cancer patients

Secondary objectives

- Assess dose response
- Establish dosing guidelines (eg, dose titration)
- Define safety profile

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

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The information in this section is based on a double-blind, placebo-controlled study of ACTIQ for the treatment of BTCP. The study was conducted at 23 sites. The first 2 studies in the cancer pain program for ACTIQ were blinded titration studies. These studies provided identical instructions where patients titrated to an individualized dose of ACTIQ that provided meaningful pain relief with acceptable side effects. These studies demonstrated that the successful dose of ACTIQ was best determined by titration and could not be predicted by other factors (eg, dose of the ATC medication). Based on experience from these studies, a third controlled study was designed where patients titrated under open-label conditions that would more closely model routine clinical use. Once patients had titrated to an effective dose of ACTIQ, the efficacy of ACTIQ compared with placebo was demonstrated in a double-blind fashion.

Design

This was a multicenter, double-blind, randomized, placebo-controlled crossover study.

Patient Completion Status

	No.	%
Received drug and entered titration phase	130	100%
• Withdrew due to AE in titration phase	22	17%
• Withdrew due to other reason in titration phase	15	12%
• Completed titration phase	93	72%
Completed titration phase and entered double-blind phase	92	100%
• Withdrew due to AE in double-blind phase	7	8%
• Withdrew due to other reason in double-blind phase	13	14%
• Completed 10 episodes in double-blind phase	72	78%

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

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Titration Phase

Of the 130 patients enrolled in the study, 93 patients (72%) found an effective ACTIQ dose during dose titration, and 37 patients (29%) withdrew from the study. Of the 37 withdrawals during the titration phase, 22 patients (17%) withdrew due to an adverse event. Twelve of these patients experienced adverse events that were considered by the investigators to be unrelated or unlikely related to ACTIQ. Study drug related adverse events that resulted in withdrawal were typical opioid-related events such as nausea, dizziness, and itching.

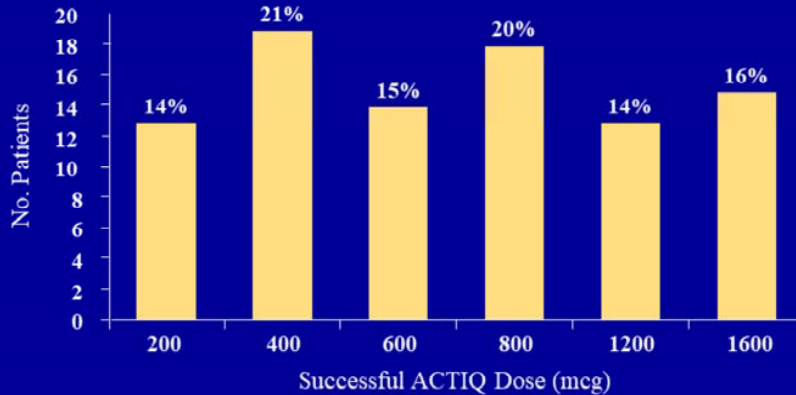
Fifteen patients (12%) withdrew during the titration phase for other reasons. One-third of these patients (5/15) withdrew because of their unwillingness or inability to complete the study diaries. Four patients had changes (cessation or decrease) in their breakthrough pain. Other reasons for withdrawal included inadequate pain relief, preference for regular supplemental medication, dislike of ACTIQ taste, failure to use ACTIQ, patient move, and patient request. One patient successfully completed the titration phase but did not enter the double-blind phase for reasons unrelated to the study drug.

Double-Blind Phase

Ninety-two patients entered the double-blind phase of the study. Of these 92 patients, 72 patients (78%) completed the study, and 20 patients (22%) withdrew. Of the 20 withdrawals during this phase, 7 patients (8%) withdrew due to an adverse event (6 were unrelated to study drug, 1 had itching and urticaria). Thirteen patients (14%) withdrew for reasons other than an adverse event. Eight of these patients were withdrawn because they did not use all 10 units within the 14 days specified in the protocol. Two patients were withdrawn at the time that the sponsor closed the study. Other reasons included preference for previous supplemental medication, radiotherapy, and patient request.

Distribution of Successful ACTIQ Doses* in Patients Entering Double-Blind Phase

N=92



*A successful dose of ACTIQ was defined as a dosage strength where 1 unit of ACTIQ could be used consistently for at least 2 consecutive days to treat breakthrough cancer pain without unacceptable side effects.

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

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All ACTIQ dose strengths (200 mcg-1600 mcg) were used in the study. The patients' successful doses were evenly distributed among each of the unit dose strengths (percentages ranged from 14% of the patients using the 200-mcg and 1200-mcg dose strengths to 21% of the patients using the 400-mcg dose strength).

The patients who entered the double-blind phase titrated to a mean \pm SD dose of 789 \pm 468 mcg.

The successful dose of ACTIQ for BTCP is determined by dose titration and could not be predicted by dosage of long-acting opioid.

A successful dose of ACTIQ was defined as a dosage strength where 1 unit of ACTIQ could be used consistently for at least 2 consecutive days to treat BTCP without unacceptable side effects.

Medication Performance

- Global satisfaction score (scale 0-4) was significantly higher with ACTIQ than usual supplemental medications
 - 1.98 vs 1.19 ($P=0.0001$)
- 92% of eligible patients chose to continue using ACTIQ
 - 74/80 patients chose ACTIQ long-term study
 - 6 patients returned to usual supplemental medication

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

ACT 227

ACTIQ produced a significantly higher mean medication performance rating than the placebo during the double-blind phase of the study (1.98 vs 1.19; $P<0.0001$, 3-way ANOVA). The patients in this study also demonstrated their satisfaction with ACTIQ by electing to enroll in a subsequent study. Eighty patients who successfully completed this study were eligible to enter a long-term safety study in which they could continue using ACTIQ for the treatment of their breakthrough pain. Of these 80 patients, 74 patients (92%) chose to enter the long-term study, and 6 patients declined.

Adverse Events

The Most Common Adverse Events in All 130 Patients*

Dizziness	22	(17%)
Nausea	17	(13%)
Somnolence	11	(8%)
Constipation	7	(5%)
Asthenia	6	(5%)
Confusion	5	(4%)

*Considered by the investigators to be at least possibly related to ACTIQ.

Of the 130 patients, 11 patients withdrew with adverse events possibly related to ACTIQ.

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

ACT 227

The most common ACTIQ-related adverse events for the 130 patients (adverse events that occurred on days ACTIQ was taken and that were reported by the investigator as possibly, probably, or almost certainly related to ACTIQ) were dizziness (17%), nausea (13%), and somnolence (8%). Other adverse events related to ACTIQ occurring in $\geq 3\%$ of the patients were asthenia (5%), constipation (5%), confusion (4%), vomiting (3%), and pruritus (3%). Most adverse events related to ACTIQ were mild in severity.

Of the 130 patients enrolled, 29 patients withdrew because of an adverse event. Eleven patients withdrew for an adverse event at least possibly related to ACTIQ. Nausea was the most common adverse event reported in the patients who withdrew from the study.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

Summary – Placebo-Controlled Study

- ACTIQ was more effective than placebo for breakthrough pain in cancer patients receiving oral opioids or transdermal fentanyl
- The successful dose of ACTIQ is determined by titration and cannot be predicted by the baseline opioid dose
- The most common side effects – dizziness, somnolence, and nausea – are typical of opioids and did not limit ACTIQ use
- Patient acceptance of ACTIQ for breakthrough cancer pain was high
 - 74/80 patients chose to continue taking ACTIQ for breakthrough pain

Farrar JT, et al. *J Natl Cancer Inst.* 1998;90(8):611-616. Data on file, Cephalon, Inc.

ACT 227

The open label titration process in the first phase of this study closely models that expected in routine clinical practice. The results of this double-blind, placebo-controlled study are as follows:

- After titration to the optimal dose, ACTIQ is significantly more effective than placebo for the treatment of breakthrough pain in cancer patients taking oral or transdermal opioids
- The successful dose of ACTIQ for breakthrough pain is determined by dose titration and cannot be predicted by the baseline ATC opioid dose
- The most common side effects dizziness, nausea, and somnolence did not limit ACTIQ use
- Patient acceptance of ACTIQ for BTCP is high with 74/80 patients choosing to continue to receive ACTIQ in a long-term study

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Clinical Trials
Long-Term Safety Study

ACT 227

Study Design and Objective

Design

- Multicenter, open-label, long-term study

Objective

- To evaluate the long-term safety and tolerance of ACTIQ for the treatment of breakthrough pain in cancer patients who were previously enrolled in other ACTIQ studies

Payne R, et al. *J Pain Symptom Manage.* 2001;22(1):575-583.

ACT 227

This section includes data from patients who enrolled in the long-term study and who had completed a 4-month block of study participation or had withdrawn since 7/15/96 and before 11/15/96. Some slides in this module contain updated data (from patients who had completed a 4-month block of study participation or had withdrawn since 11/15/96 and before 6/15/98). These data are footnoted on module slides and are discussed in italicized font in the module text.

Design

This was a multicenter, open-label, long-term study. The study was approved by the institutional review boards at all sites and all patients gave written, informed consent prior to participation.

Objective

The objective of the study was to evaluate the long-term safety of ACTIQ in patients with BTCP.

ACTIQ Use

N=155

- 41,766* ACTIQ units used
 - Mean number units/patient=277
- 38,595* episodes of breakthrough pain treated
- Treatment ranged from 1 to 423 days* (mean 91 days)

*As of 6/15/98, 155 patients had used 74,729 units to treat 69,260 episodes of breakthrough pain. Maximum length of treatment ranged from 1 to 974 days (mean 149 days).

Payne R, et al. *J Pain Symptom Manage.* 2001;22(1):575-583.

ACT 227

ACTIQ Use

Dosing data are available for 151 of the 155 patients (97%). Patients used 41,766 ACTIQ units to treat 38,595 episodes of breakthrough pain, which is slightly more than 1 unit (1.08) per episode. The duration of ACTIQ treatment ranged from 1 to 423 days (mean 91 days).

As of 6/15/98, 155 patients had used 74,729 ACTIQ units to treat 69,260 episodes of breakthrough pain. The maximum length of ACTIQ treatment was 974 days (mean 149).

Experience with ACTIQ

n=151 (of the total 155 enrolled)

- On average, 2.9 breakthrough pain episodes/day
- 2.4 breakthrough pain episodes/day were treated with ACTIQ
- 66% of patients remained on the same or a lower dose of ACTIQ during the study

Payne R, et al. *J Pain Symptom Manage*. 2001;22(1):575-583.

ACT 227

Ninety-two patients (61%) remained on the same ACTIQ dose throughout the study (ie, they remained on the same dose that they had used during their previous short-term ACTIQ study). This suggests that significant tolerance to ACTIQ does not develop over time. Seven patients (5%) ended the study on a lower dose of ACTIQ, and 52 patients (34%) ended the study on a higher dose. An ACTIQ dose increase during the study was generally attributed to disease progression and increased pain.

Patients consistently gave ACTIQ high global satisfaction ratings. The mean medication performance score for ACTIQ was consistently above 3, indicating very good to excellent relief.

The objective of the study was to evaluate the long-term safety of ACTIQ in patients with BTCP.

Adverse Events

Most Common Adverse Events*

Somnolence	14	(9%)
Constipation	13	(8%)
Nausea	12	(8%)
Dizziness	12	(8%)
Vomiting	8	(5%)

*At least possibly related to ACTIQ.

Payne R, et al. *J Pain Symptom Manage.* 2001;22(1):575-583.

ACT 227

The most common ACTIQ-related adverse events* during the study were somnolence (9%), constipation (8%), nausea (8%), dizziness (8%), and vomiting (5%). These adverse events are typical of the adverse events associated with the use of other opioids.

It is important to note that throughout the study patients continued to take their ATC medication and, if desired, their regular rescue medication. Hence, patients could have been exposed to as many as 3 opioids on any given day, which complicated the assessment of causality when an adverse event occurred.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

*An adverse event related to ACTIQ was an adverse event that occurred on days ACTIQ was taken and that were reported by the investigator as possibly, probably, or almost certainly related to ACTIQ.

Summary – Long-Term Safety Study

- In this clinical study
 - Over 41,500 units were used
 - Over 38,500 breakthrough pain episodes were treated
 - Up to 423 days of ACTIQ therapy
- ACTIQ was well tolerated
 - Side effects were typical of those associated with opioids
 - Few withdrawals due to adverse events

Payne R, et al. *J Pain Symptom Manage.* 2001;22(1):575-583.

ACT 227

Study Results

In this clinical study

- Over 41,500 ACTIQ units were used
- More than 38,500 episodes of breakthrough pain were treated
- Up to 423 days of ACTIQ therapy
- Very few withdrawals due to adverse events related to ACTIQ

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Safety Profile

ACT 227

Clinical Trial Results

- ACTIQ was generally well tolerated in opioid tolerant cancer patients
- Opioid side effects should be expected and managed accordingly
- All patients should be followed for serious opioid adverse effects
 - Respiratory depression (potentially leading to apnea or respiratory arrest)
 - Circulatory depression
 - Hypotension
 - Shock

ACT 227

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

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

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

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

Short-Term Clinical Trials

- Inconclusive dose-response relationship due to study design
 - Use of concomitant opiates for persistent cancer pain
 - Titration schemes used
- Adverse events (AEs) were included regardless of causality
- No reports of serious AEs (eg, respiratory depression)
- Reported AEs from these trials
 - Nausea
 - Somnolence
 - Dizziness
 - Vomiting

Portenoy RK, et al. *Pain*. 1999;79:303-312. Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245. Farrar JT, et al. *J Natl Cancer Inst*. 1998;90(8):611-616.

ACT 227

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and BTCP. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of ACTIQ that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies. Adverse events are listed in descending order of frequency within each body system.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

Long-Term Clinical Trial

- 155/257 patients in the short-term clinical trial continued into the long-term study*
- Average length of treatment was 129 days
- Generally, the adverse events profile was similar to those experienced in the the short-term studies

*Data available for 151 patients.

Payne R, et al. *J Pain Symptom Manage.* 2001;22(1):575-583.

ACT 227

A long-term extension study was conducted in 155 patients with malignancy and BTCP who were treated for an average of 129 days. Data are available for 151 of these patients. Table 4 of the package insert lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse events are listed in descending order of frequency within each body system.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.¹³

The most common side effects observed were somnolence, nausea, vomiting, and dizziness.

Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose.

General Safety Considerations*

- The most serious adverse events associated with all opioids are respiratory depression, circulatory depression, hypotension and shock. All patients should be followed for respiratory depression
- The most common adverse events observed in ACTIQ clinical trials were somnolence, nausea, vomiting and dizziness
- Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose
- Individual titration to ensure adequate analgesia and minimal side effects
- Limit consumption to 4 or fewer units/day

*See ACTIQ package insert, including boxed warning, for full prescribing information.

ACT 227

PRECAUTIONS

General

The initial dose of ACTIQ to treat episodes of BTCP should be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

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

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer. Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid nontolerant patients.

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

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

General Safety Considerations (cont.)

- Opioids may impair mental/physical ability required for the performance of potentially dangerous tasks (eg, driving a car, operating heavy machinery)
- Concomitant use of central nervous system active drugs requires special patient care and observation

*See ACTIQ package insert, including boxed warning, for full prescribing information.

ACT 227

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (eg, driving a car or operating machinery). Patients taking ACTIQ should be warned of these dangers and should be counseled accordingly. The use of concomitant CNS active drugs requires special patient care and observation.

Precautions – Dental Decay

- Frequent consumption of sugar-containing products may increase the risk of dental decay (each ACTIQ unit contains 2 grams of sugar [hydrated dextrans])
- The occurrence of dry mouth associated with the use of opioid medications may add to this risk
- Postmarketing reports of dental decay, including dental caries, tooth loss and gum line erosion, have been received in patients taking ACTIQ
- In some of these patients, dental decay occurred despite reported routine oral hygiene
- Patients using ACTIQ should consult their dentist to ensure appropriate oral hygiene

*See ACTIQ package insert, including boxed warning, for full prescribing information.

ACT 227

PRECAUTIONS – Information for Patients and Their Caregivers

Dental Decay

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

Postmarketing reports of dental decay have been received in patients taking ACTIQ (see **ADVERSE REACTIONS – Postmarketing Reports**). In some of these patients, dental decay occurred despite reported routine oral hygiene. Therefore, patients using ACTIQ should consult their dentist to ensure appropriate oral hygiene.

Precautions – Diabetic Patients

- Each ACTIQ unit contains 2 grams of sugar (hydrated dextrans)
- Diabetic patients should be aware of the sugar content in ACTIQ and discuss with their prescribing physician

ACT 227

PRECAUTIONS – Information for Patients and Their Caregivers

Diabetic patients should be advised that ACTIQ contains approximately 2 grams of sugar per unit. Patients should discuss this with their prescribing physician.

Precautions – Special Populations

- Precautions regarding the use of ACTIQ in these special populations who are or who suffer from
 - Geriatric
 - Cardiac disease
 - Hypoventilation (respiratory depression)
 - Hepatic/renal disease
 - Chronic pulmonary disease
 - Head injuries/increased intracranial pressure

ACT 227

Geriatric Use

Of the 257 patients in clinical studies of ACTIQ used for the treatment of BTCP, 61 (24%) were 65 and over, while 15 (6%) were 75 and over.

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

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

Cardiac Disease

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

Hypoventilation (Respiratory Depression)

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

Hepatic or Renal Disease

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

Chronic Pulmonary Disease

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

Head Injuries and Increased Intracranial Pressure

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

Precautions – Drug Interactions

- No formal drug interaction studies have been performed with ACTIQ
- No *in vitro* or *in vivo* studies have been conducted to assess the impact of potential interactions on the administration of ACTIQ
- Fentanyl is metabolized in the liver and intestinal mucosa into norfentanyl by the cytochrome P450 (CYP) 3A4 enzyme
- Administration of ACTIQ with drugs that inhibit or induce CYP3A4 enzyme may affect the bioavailability and systemic clearance of fentanyl
- Dose of ACTIQ may need to be adjusted accordingly

ACT 227

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450 3A4 isoform. Drugs that inhibit P450 3A4 activity may increase the bioavailability of swallowed fentanyl (by decreasing intestinal and hepatic first-pass metabolism) and may decrease the systemic clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Drugs that induce cytochrome P450 3A4 activity may have the opposite effects. However, no *in vitro* or *in vivo* studies have been performed to assess the impact of those potential interactions on the administration of ACTIQ.

Precautions – Drug Interactions (cont.)

- The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, potent inhibitors of cytochrome P450 3A4 isoform and alcoholic beverages may produce increased depressant effects
- ACTIQ is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics

ACT 227

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450 3A4 isoform. Drugs that inhibit P450 3A4 activity may increase the bioavailability of swallowed fentanyl (by decreasing intestinal and hepatic first-pass metabolism) and may decrease the systemic clearance of fentanyl. The expected clinical results would be increased or prolonged opioid effects. Drugs that induce cytochrome P450 3A4 activity may have the opposite effects. However, no *in vitro* or *in vivo* studies have been performed to assess the impact of those potential interactions on the administration of ACTIQ.

Precautions — Drug Interactions (cont.)

- Drugs that inhibit CYP3A4 enzyme may increase bioavailability of swallowed fentanyl and decrease its systemic clearance
- The expected clinical outcome would be increased and prolonged opioid effects
- Examples of such drugs include
 - Macrolide antibiotics (eg, erythromycin)
 - Azole antifungal agents (eg, ketoconazole, itraconazole)
 - Protease inhibitors (ritanovir)
- The dose of ACTIQ may need to be reduced

ACT 227

Patients who begin or end therapy with potent inhibitors of P450 3A4 such as macrolide antibiotics (eg, erythromycin), azole antifungal agents (eg, ketoconazole and itraconazole), and protease inhibitors (eg, ritanovir) while receiving ACTIQ should be monitored for a change in opioid effects and, if warranted, the dose of ACTIQ should be adjusted.

Precautions – Drug Interactions (cont.)

- Drugs that induce CYP3A4 enzyme may decrease bioavailability of swallowed fentanyl and increase its systemic clearance
- The expected clinical outcome would be decreased and opioid effects would also be shortened
- Examples of such drugs include
 - Anticonvulsants (eg, phenobarbital, phenytoin, carbamazepine)
- The dose of ACTIQ may need to be increased

ACT 227

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450 3A4 isoform. Drugs that induce CYP3A4 enzyme activity may decrease bioavailability of swallowed fentanyl and increase its systemic clearance. The expected clinical result would be decreased or shortened opioid effects. Thus patients that begin or end therapy with potent inducers of CYP3A4 such as anticonvulsants (eg, phenobarbital, phenytoin, and carbamazepine) while receiving ACTIQ may need to be monitored for a change in opioid effects and, if warranted, the dose of ACTIQ may need to be increased.

However, no *in vitro* or *in vivo* studies have been performed to assess the impact of these potential interactions on the administration of ACTIQ.

Potential for Abuse and Diversion

- ACTIQ is a Schedule II controlled substance
- ACTIQ may be habit forming
- ACTIQ must be stored and disposed of properly
- ACTIQ is to be used only by the patient for whom it is dispensed
- Fear of tolerance and possible addiction should not deter the use of doses that adequately relieve pain in cancer patients

ACTIQ Package Insert. Rev. Aug. 2004. ACTIQ Patient Leaflet. Rev. Aug. 2004.

ACT 227

ACTIQ is a Schedule II controlled substance that may be habit forming. ACTIQ is to be used only by the patient for whom it is dispensed and unused ACTIQ units must be disposed of properly. Fear of tolerance and addiction, however, should not deter the use of doses that adequately relieve pain in cancer patients.

Summary – Safety Profile

- The most serious adverse events associated with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. All patients should be followed for symptoms of respiratory depression
 - Adverse events seen with ACTIQ are typical opioid side effects
 - The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting and dizziness
 - Frequently, adverse events will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose
 - No serious adverse events were reported in clinical trials

ACT 227

Important Warnings

- Indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain**
- Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain
- This product **must not** be used in opioid nontolerant patients
- Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer
- Instruct patients/caregivers that ACTIQ can be fatal to a child. Keep all units from children and discard properly
- The most common side effects observed were somnolence, nausea, vomiting, and dizziness
- ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain

Summary – Safety Profile (cont.)

- Caution should be exercised regarding the use of ACTIQ in certain patient populations (eg, geriatric, hepatic and/or renal insufficiency)
- The risk management program has been designed to address 3 key potential risk situations
 - Accidental ingestion in children
 - Prescribing for use by opioid nontolerant patients
 - Abuse and diversion

ACT 227

Important Warnings

- Indicated only for the management of breakthrough cancer pain in patients with malignancies who are **already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain**
- Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain
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- Instruct patients/caregivers that ACTIQ can be fatal to a child. Keep all units from children and discard properly
- The most common side effects observed were somnolence, nausea, vomiting, and dizziness
- ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Risk Management Program
(RMP)

ACT 227

ACTIQ Risk Management Program (RMP)

- Benefits of ACTIQ come with potential risks
- RMP objective is to ensure safe use of the product
- The RMP has been designed to address 3 key potential risk situations
 - Accidental ingestion in children
 - Prescribing for use by opioid nontolerant patients
 - Abuse and diversion

Data on file, Cephalon, Inc.

ACT 227

As with other potent opioids, the analgesic benefits to cancer pain patients offered by ACTIQ are accompanied by risks when the product is misused or abused. This use in populations for whom the product was not intended includes the accidental ingestion in children, use in opioid nontolerant patients (inappropriate patient selection), and diversion by individuals who abuse controlled substances. Cephalon, Inc., has developed a comprehensive program for ACTIQ that addresses the risk of the potential untoward events in the unintended populations to the extent possible. The purpose of this section is to describe elements of the ACTIQ Risk Management Program.

The goal of the ACTIQ Risk Management Program is to help ensure the safe use of ACTIQ and other potentially toxic medications in the home, thereby protecting availability of ACTIQ for cancer patients who need it. To this end, an RMP was developed that provides appropriate child safety protections, emphasizes the approved indication, and minimizes diversion and abuse. Multiple steps are taken to minimize the risk of accidental ingestions, especially by children who may find the dosage unit to be appealing.

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

Fentanyl is a Schedule II opioid and thus, has the potential for diversion and abuse, which is the third general area addressed in the ACTIQ Risk Management Program.

ACTIQ RMP Key Elements

- Product- and package-specific design features
 - Child-resistant unit-dose packaging
 - Dosage strength marked on both the ACTIQ lozenge and handle
 - Safety icons appear throughout
- Prominent labeling for professionals, patients, and caregivers
- Welcome kit containing introductory educational and safety materials for patients and/or their caregivers
- Professional, patient, caregiver, and child education programs
- Intervention at the point of dispensing

Data on file, Cephalon, Inc.

ACT 227

The ACTIQ Risk Management Program comprises several important elements that have been designed to work together to minimize the risks associated with ACTIQ. These elements include:

- Product and packaging design features in which units are individually packaged in opaque, child-resistant blister packs. The drug matrix is off-white to decrease appeal to children, and the handle has a prominent warning flag to remind users that it contains a potent medication
- Strong labeling for professionals, patients, and caregivers with an emphasis on redundant key safety messages
- A welcome kit of introductory educational and safety materials including education materials such as the ACTIQ Patient Leaflet and a child safety booklet and safety materials such as a placard, emergency care instructions, and methods for secure storage
- Intervention at the point of dispensing. The outpatient or retail pharmacist will serve an important role in reinforcing safety and proper patient selection messages

ACTIQ[®] C-II
(oral transmucosal fentanyl citrate)
Dosage and Administration

ACT 227

Administration of ACTIQ

CUT

- Cut open the child-resistant blister pack only when ready to use ACTIQ
- Remove the ACTIQ unit

CONSUME

- Consume the ACTIQ unit by dissolving it in the mouth between the cheeks and gums
- Move ACTIQ around in the mouth, especially along the cheeks. Twirl the handle often. Do not bite or chew ACTIQ
- Do not eat or drink anything while taking ACTIQ

CLOCK

- Clock for 15 minutes – the recommended dosing time
- An ACTIQ unit should be completely finished in 15 minutes to get the most relief. If ACTIQ is finished too quickly, more of the medication is swallowed and the patient will receive less relief

ACT 227

Administration of ACTIQ

The blister package should be opened with scissors immediately prior to product use. The patient should place the ACTIQ unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from 1 side to the other using the handle. The ACTIQ unit should be sucked, not chewed. A unit dose of ACTIQ, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed. Patients should not bite or chew ACTIQ.

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

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

Guidelines for Proper Administration of ACTIQ

- Do not open ACTIQ until ready to use
- Handle package gently; the product may break if patient or caregiver attempts to push it through the packaging. The package must be cut open to access the product
- Patients may drink water before using ACTIQ (to moisten mouth or reduce dryness) but do not drink or eat anything while consuming ACTIQ
- Place ACTIQ unit in mouth, twirling and moving it from side to side and “painting” inside of cheek. Consume ACTIQ unit completely over 15 minutes
- ACTIQ is for one-time use only. Do NOT reuse
- Be careful not to bite or chew. Vigorous rubbing, biting or chewing may cause the lozenge to prematurely break down or be more physically irritating
- ACTIQ lozenge may crumble if not used with care and as directed
- If unable to finish entire ACTIQ unit, rinse remaining lozenge under hot water or use temporary storage container for disposal at a later time
- Dispose of handles properly (eg, out of reach of children)

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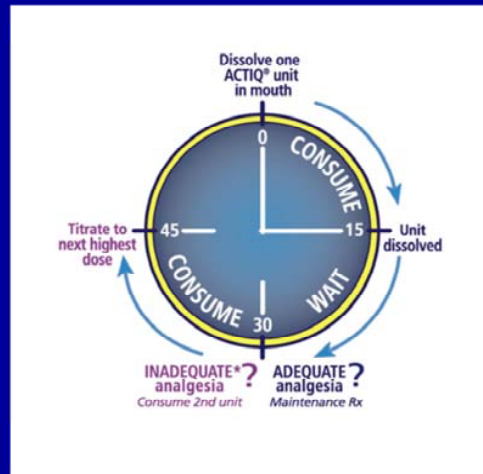
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ACTIQ Titration Process



*If treatment of several consecutive breakthrough cancer pain episodes requires more than one ACTIQ unit per episode, return to top of diagram using next highest dosage strength.

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Before starting patients on ACTIQ, it is important to discuss the titration process and tell them that it may take several adjustments in their dosage level to find the optimal balance between analgesia and side effects. The recommended starting dose of ACTIQ is 200 mcg. The initial prescription should be for 6 units.

To achieve maximum relief, patients should finish the ACTIQ unit completely in 15 minutes. If they finish too quickly, or bite and swallow the matrix, they will swallow more of the medicine and experience less relief. Longer or shorter consumption times than the recommended 15 minutes may produce less efficacy than reported in trials.

Patients should be instructed to dissolve 1 ACTIQ unit in the cheek over a 15-minute period, wait 15 minutes more, and then determine if adequate pain relief has been achieved. If so, the patient should be maintained on that dose. If not, patients should be instructed to consume a second ACTIQ unit over 15 minutes and tell their doctors.

If treatment of several consecutive breakthrough cancer pain episodes requires more than 1 ACTIQ unit per episode, return to the top of the diagram using next highest dosage strength.

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.¹³

While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child-resistant blister pack, yet may contain enough medicine to be fatal to a child.¹³

Prescribing ACTIQ – Sample Scripts

Titration Rx	
Name _____	Age _____
Address _____	Date _____
ACTIQ 200 mcg	
Disp six units	
Sig: Dissolve one unit in mouth over 15 min.	
Repeat PRN 1x 15 min after consumption of first unit	
No more than 2 units/episode	
_____ MD	
<small>Q LABEL REFILLS: _____ TIMES Q PRINT: 3 XES Prepared by: MWH/MS</small>	

Maintenance Rx	
Name _____	Age _____
Address _____	Date _____
ACTIQ 800 mcg	
Disp one hundred twenty units	
Sig: 1 unit PRN up to 4x/day	
_____ MD	
<small>Q LABEL REFILLS: _____ TIMES Q PRINT: 3 XES Prepared by: MWH/MS</small>	

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The goal of titration is to provide the patient with adequate analgesia while minimizing side effects. During the titration process, no more than 2 units should be taken for each pain episode, and once a successful maintenance dose has been found, patients should limit their consumption to 4 or fewer units per day.

Summary – ACTIQ

- Patented OTS™ designed for delivery of fentanyl
- Absorbed directly through the buccal mucosa with slow GI absorption for prolonged duration of action
- Peak plasma levels in 20-40 minutes, with a 3- to 5-minute half-life in to the CNS
- Duration of action that closely matches a BTCP episode
- Efficacy unaffected by type of long-acting pain medication
- Pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit

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- Patented OTS™ designed for delivery of fentanyl
- Rapidly absorbed through the buccal mucosa with slow GI absorption for prolonged duration of action
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Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of ACTIQ is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit of ACTIQ, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.¹³ Patients should not bite or chew ACTIQ.

Black Box Warning

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Black Box Warning

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

Actiq is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer. Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid nontolerant patients.

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

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

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