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
Cephalon
415-613-1493

Document Produced in Native Format


ACTIQ® C-II
(oral transmucosal fentanyl citrate)
ACT 227

Black Box Warning

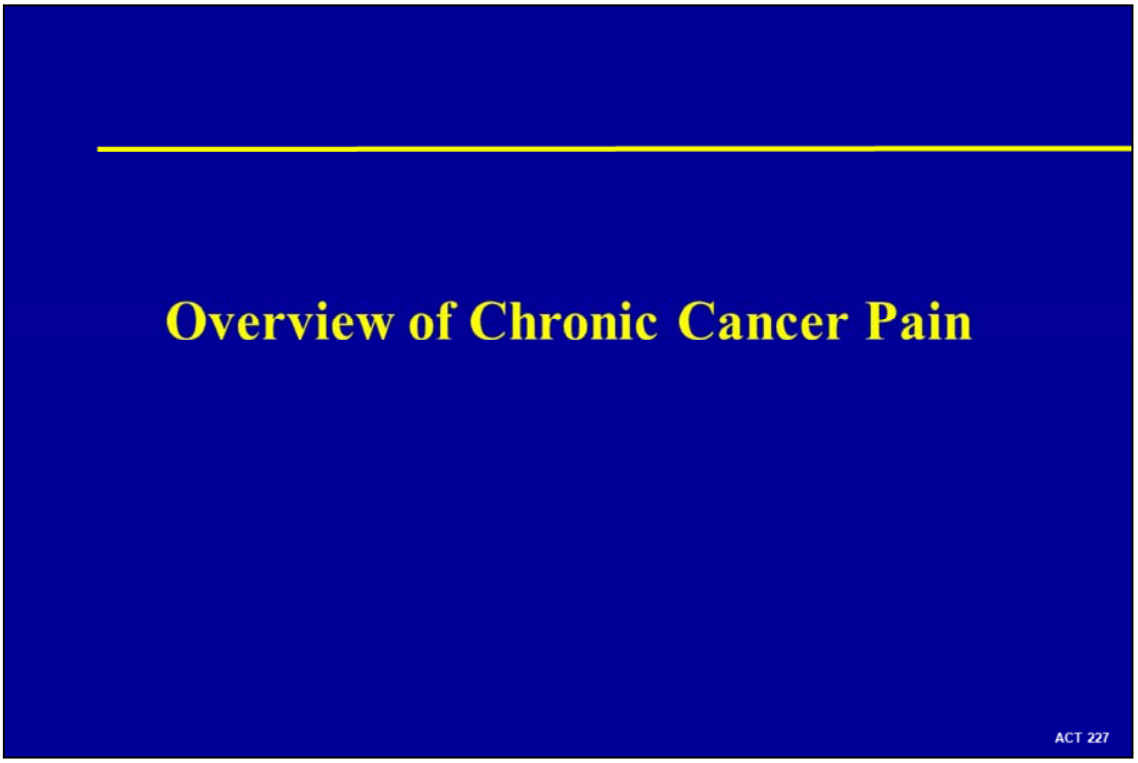
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

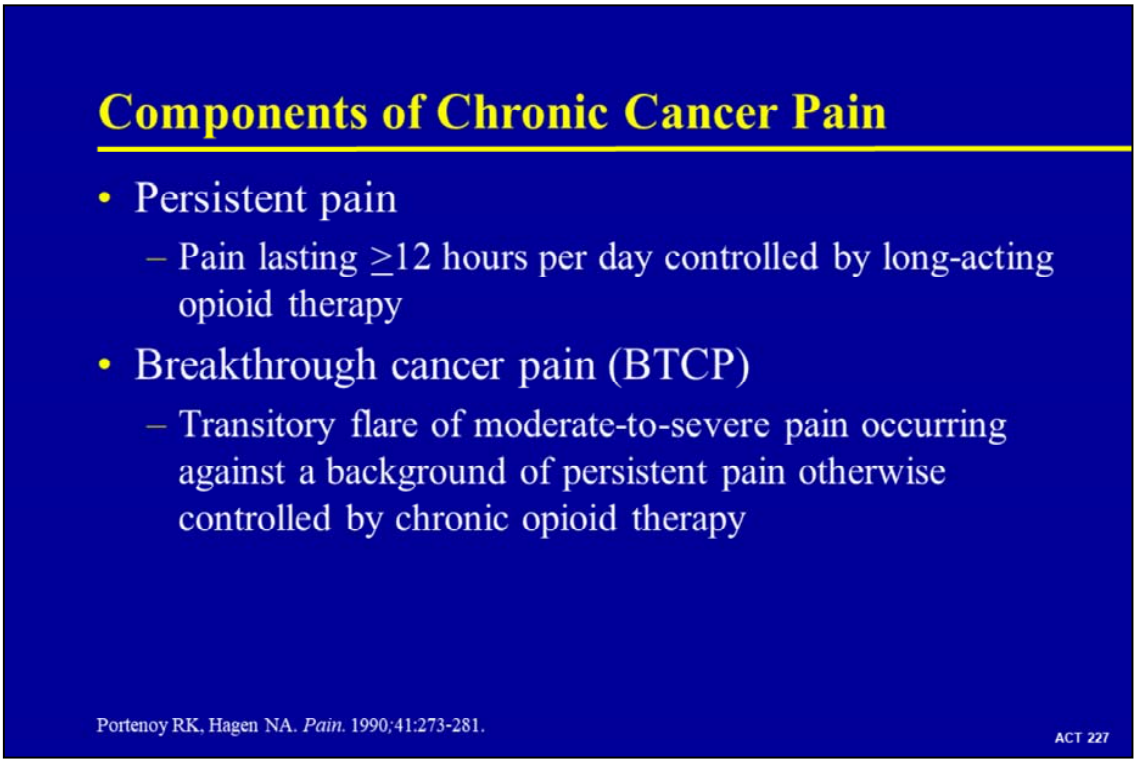
***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 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.)

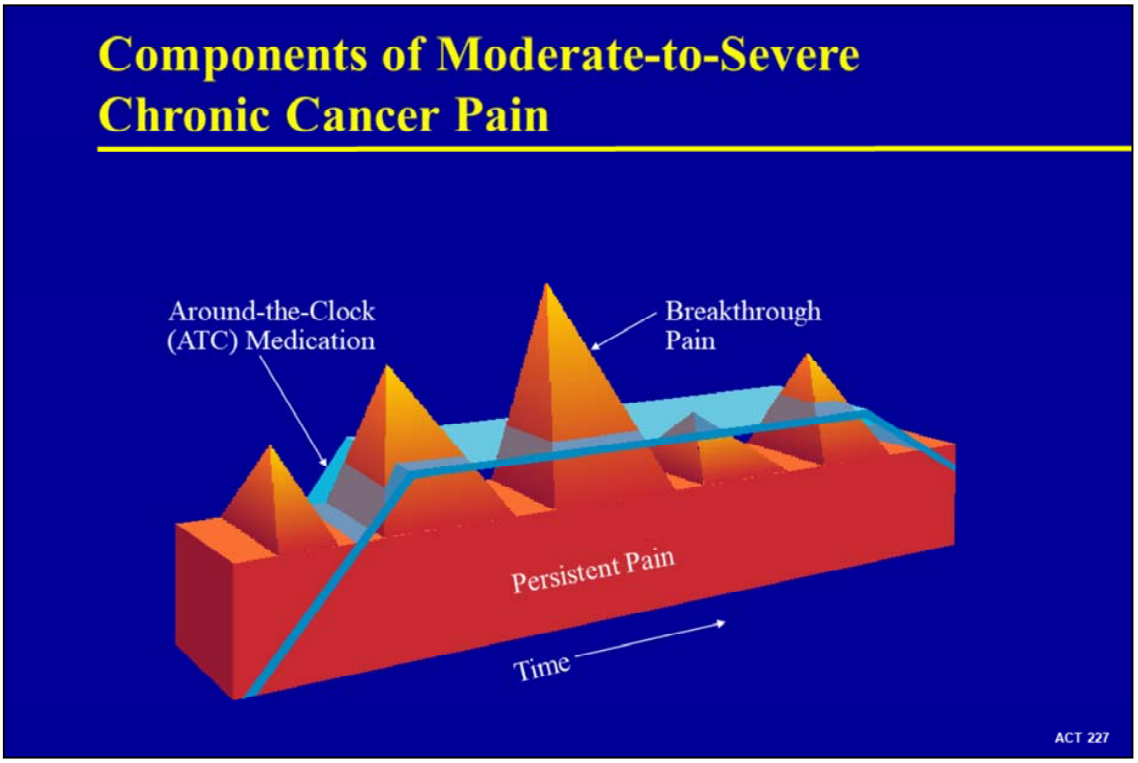
ACT 227


Overview of Chronic Cancer Pain
ACT 227

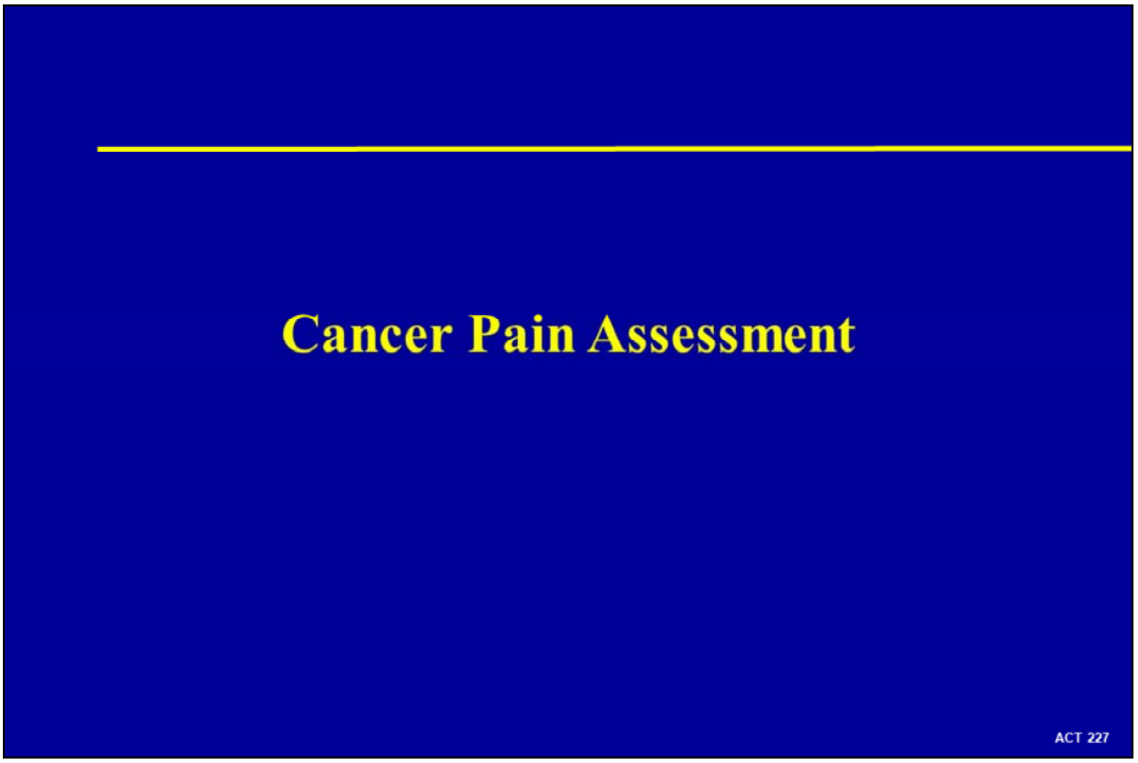


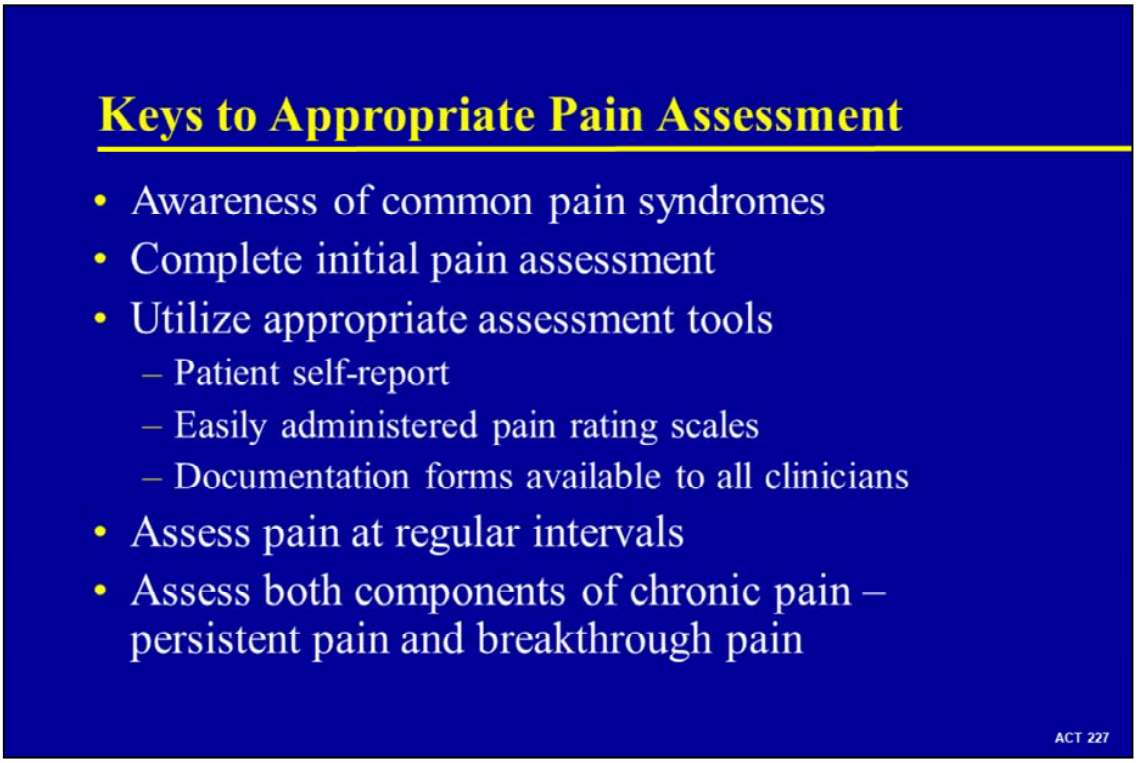
Persistent Pain—When cancer pain becomes moderate to severe, it is often present most of the time, day and night. Portenoy and Hagen defined persistent or baseline pain as pain reported by the patient as the average pain intensity experienced for 12 or more hours during the 24 hours prior to the interview.[1] 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.

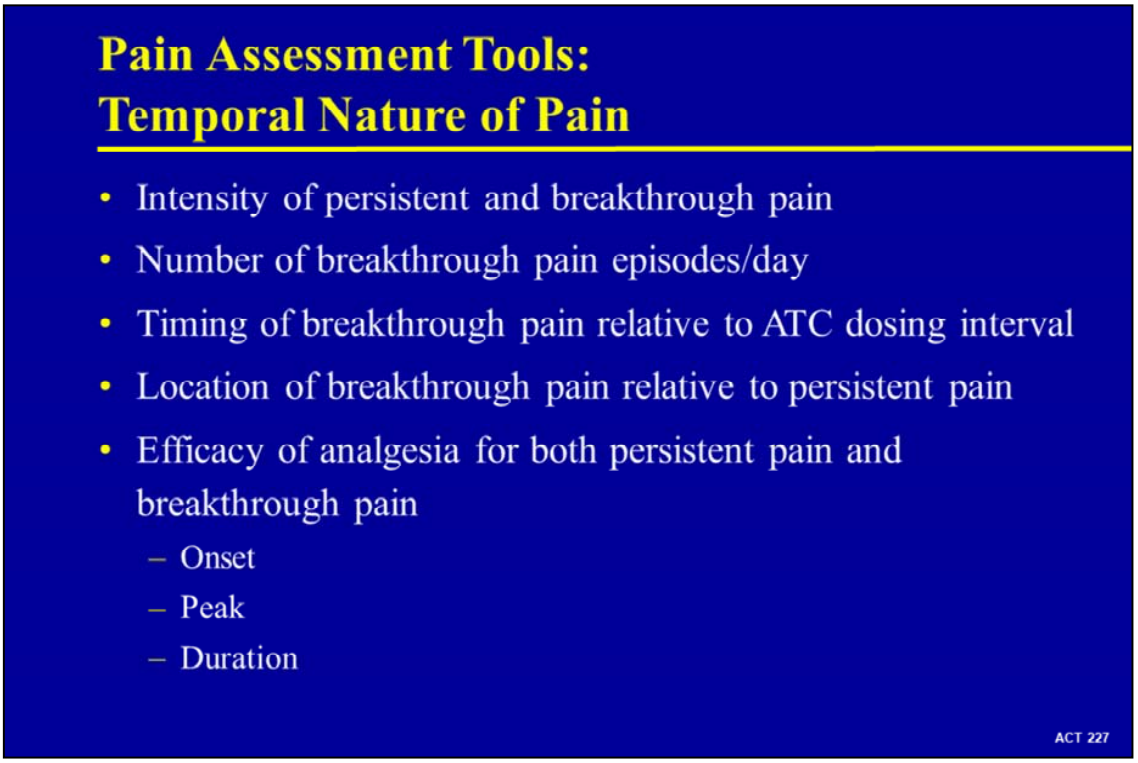


There are 2 components of chronic cancer pain; persistent cancer pain and breakthrough cancer pain (BTCP). Long-acting opioids are commonly used to manage the persistent pain. However, these medications are not indicated for the management of BTCP.


Cancer Pain Assessment
ACT 227

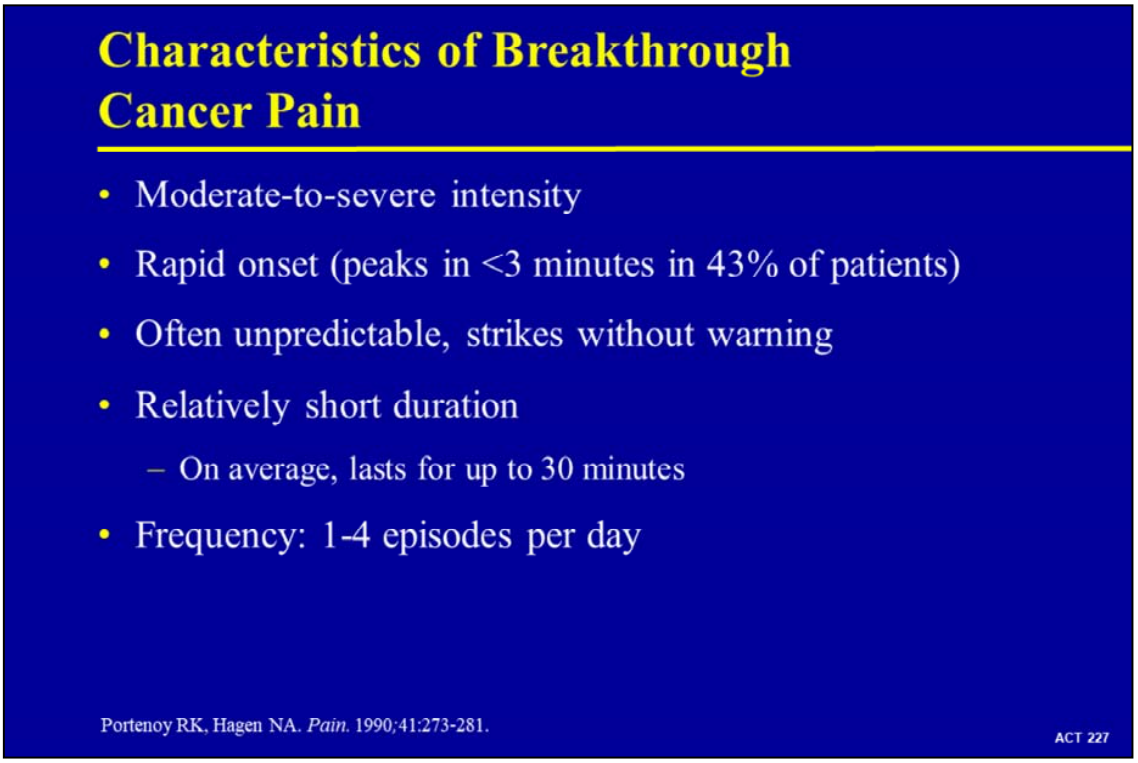


Proper assessment of cancer pain involves several steps. Clinicians must ask patients about pain and provide an initial assessment that includes a medical history, information about pain intensity and characteristics, a physical examination, a psychosocial examination, and where appropriate, a diagnostic 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 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.



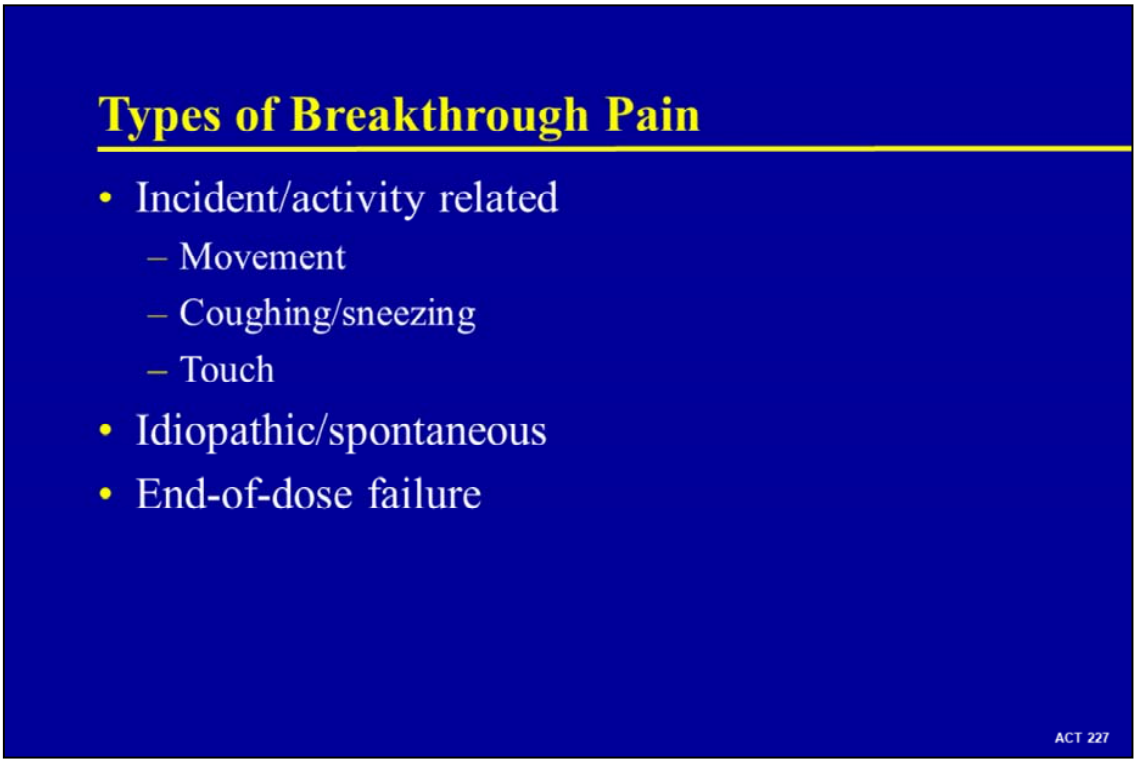
Breakthrough cancer pain is a common clinical phenomenon. Historically, BTCP has been assessed as a secondary outcome measure in studies evaluating the efficacy of an ATC medication.[3,4,5] This approach focused on end-of-dose failure and not on incident pain or idiopathic/spontaneous pain. In a study 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]

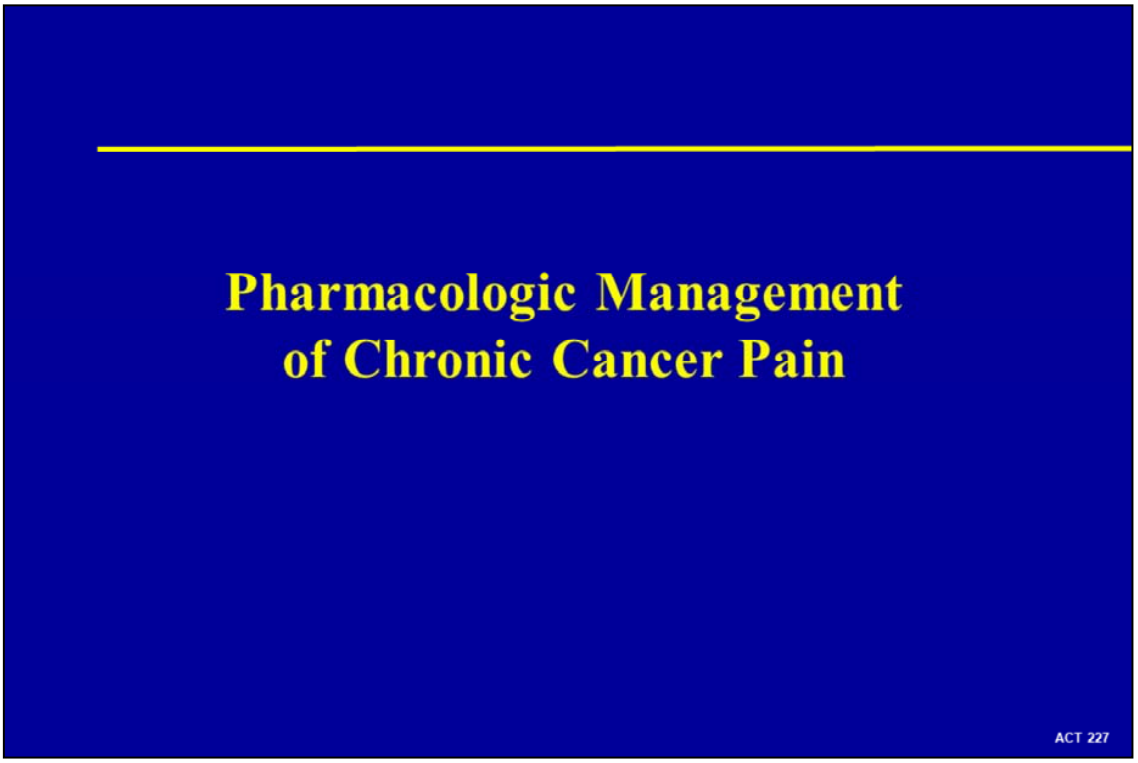


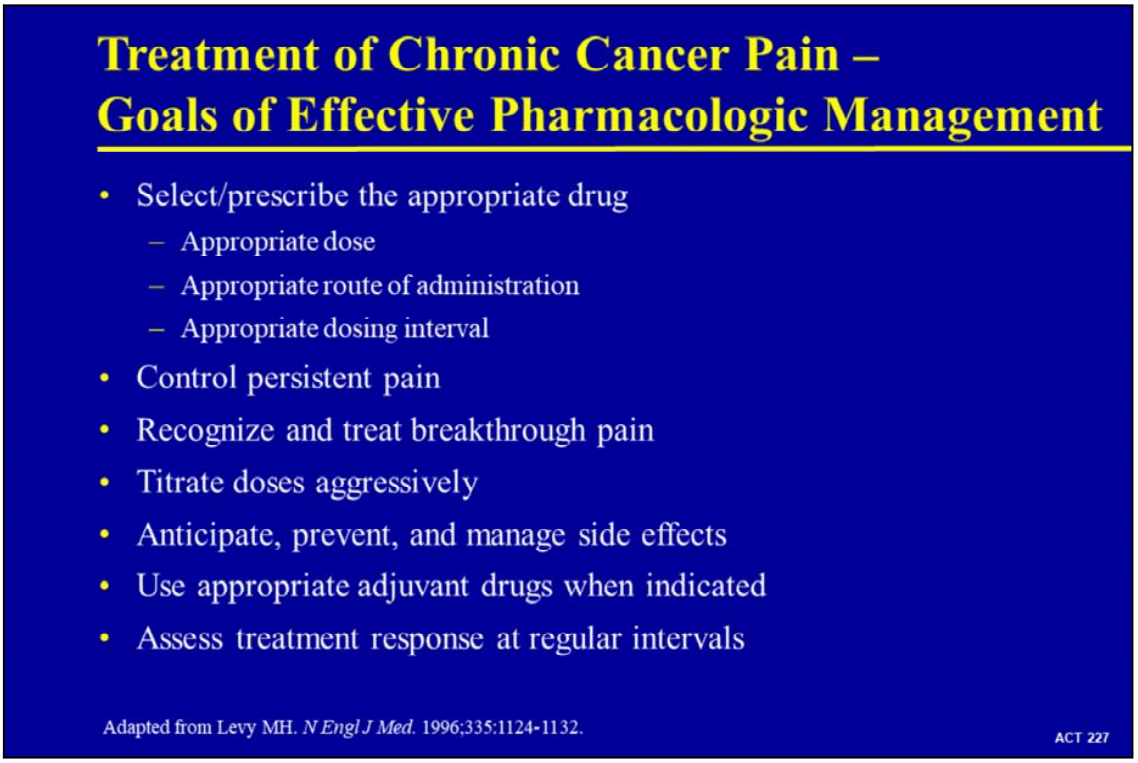
The concept of breakthrough pain has been relatively ill defined until recently. In 1990, Portenoy and Hagen published a landmark survey that has allowed investigators to use standard definitions of both breakthrough and persistent pain. Using these standardized definitions it is now possible to compare 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.

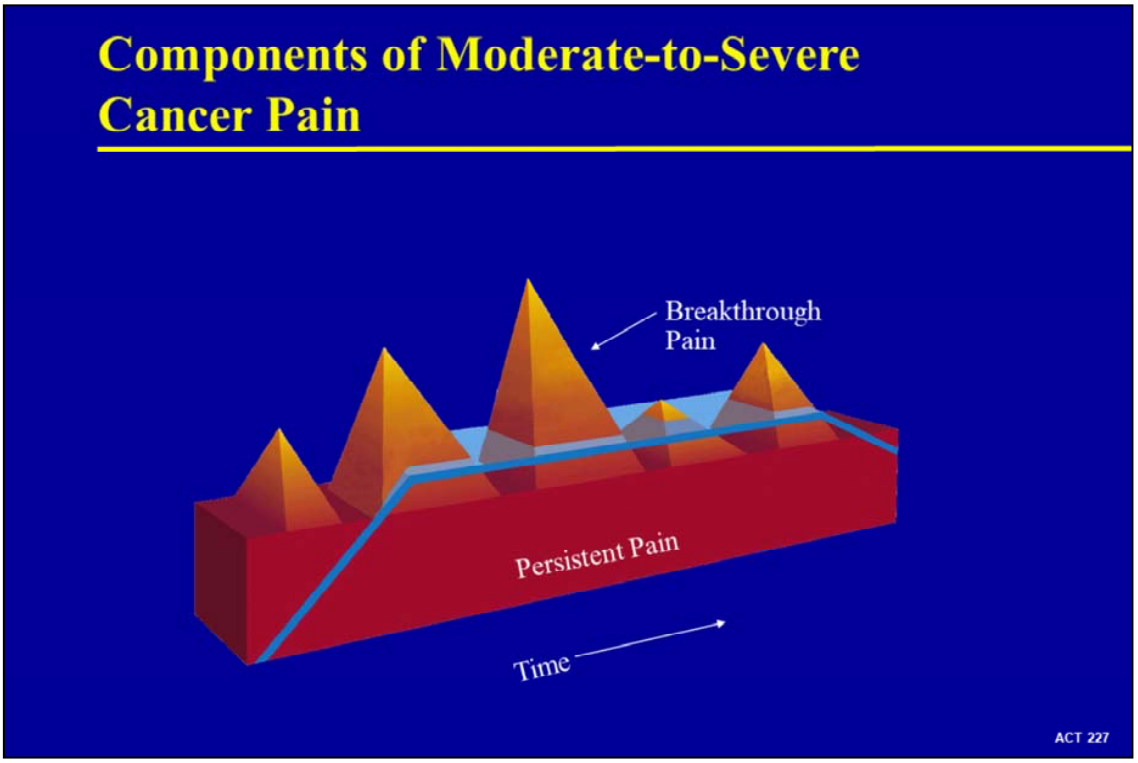

Pharmacologic Management
of Chronic Cancer Pain
ACT 227



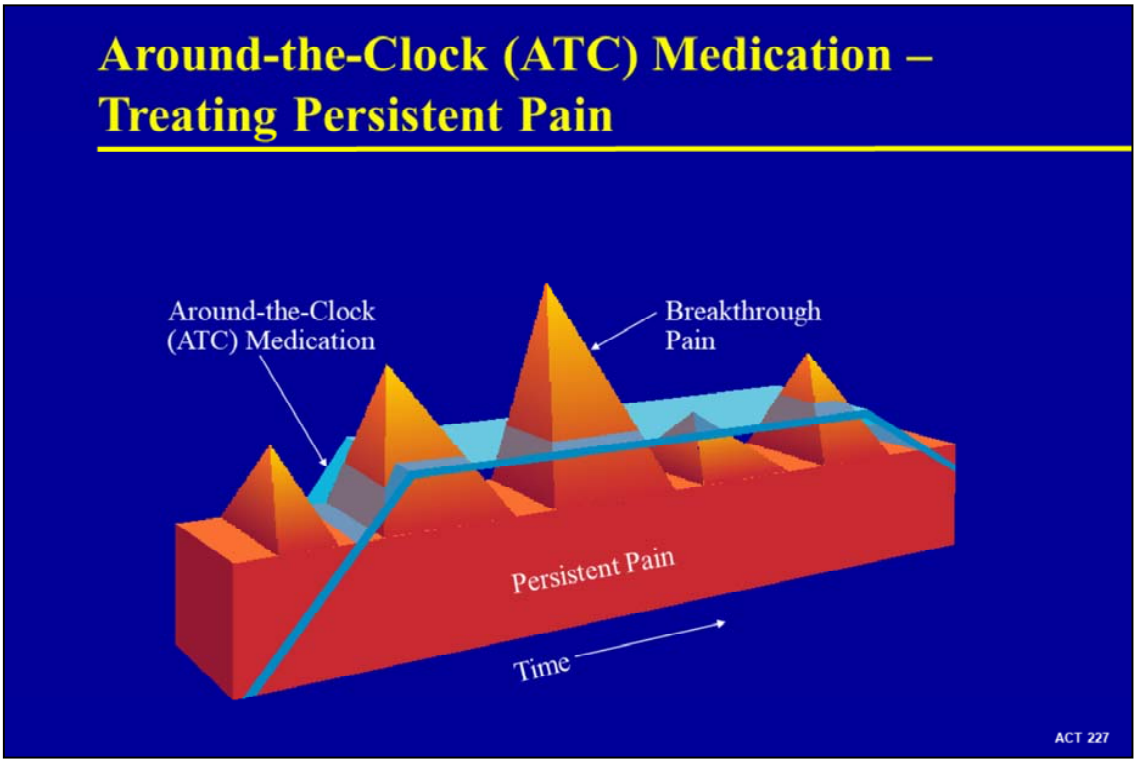
Millions of patients experience chronic cancer pain that should be adequately treated. Once pain has been properly assessed, appropriate pharmacologic management of cancer pain requires choosing an appropriate agent and route of analgesic administration, titration of dosing and manipulation of timing 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

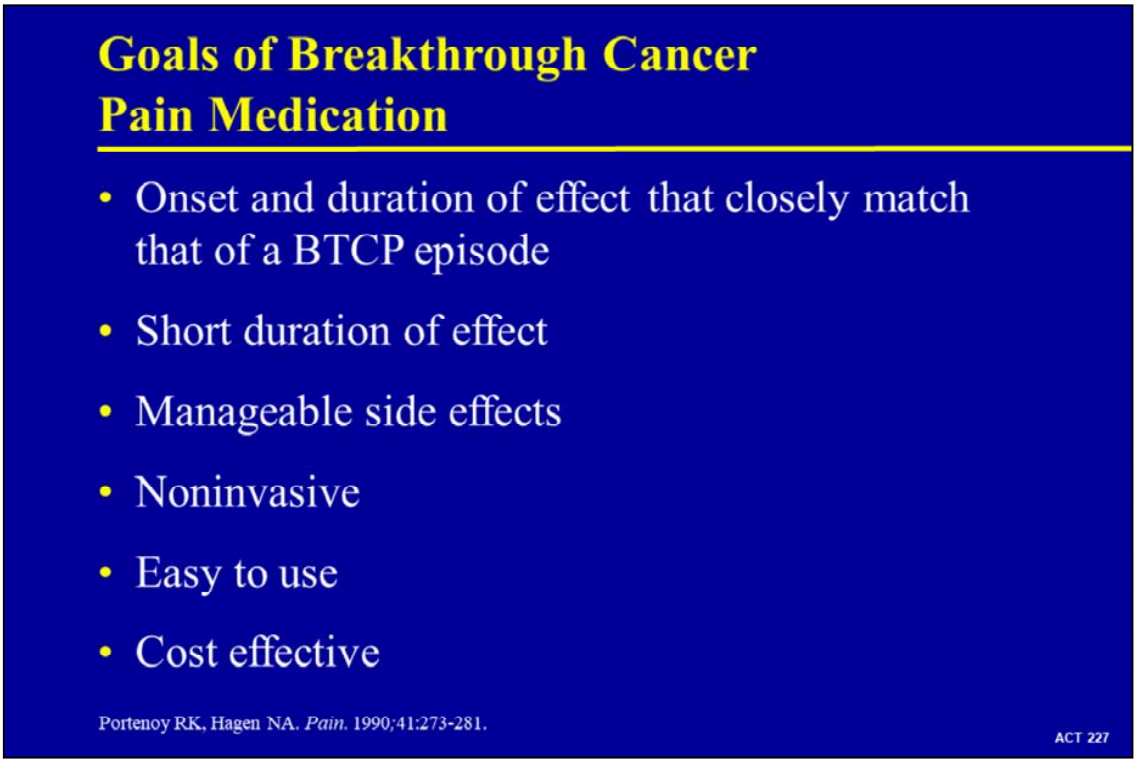
These issues will be discussed in more detail later in this slide kit.



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.



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.



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

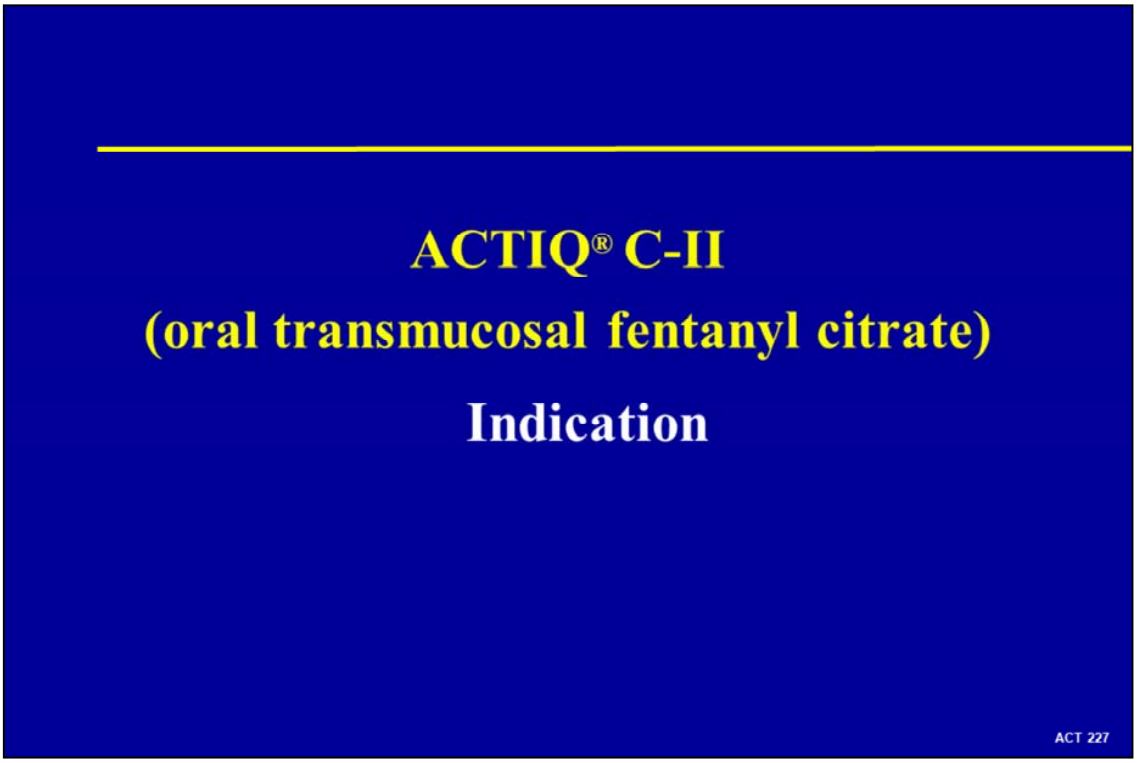
•Short duration of effect

•Manageable side effects

•Noninvasive

•Easy to use

•Cost effective

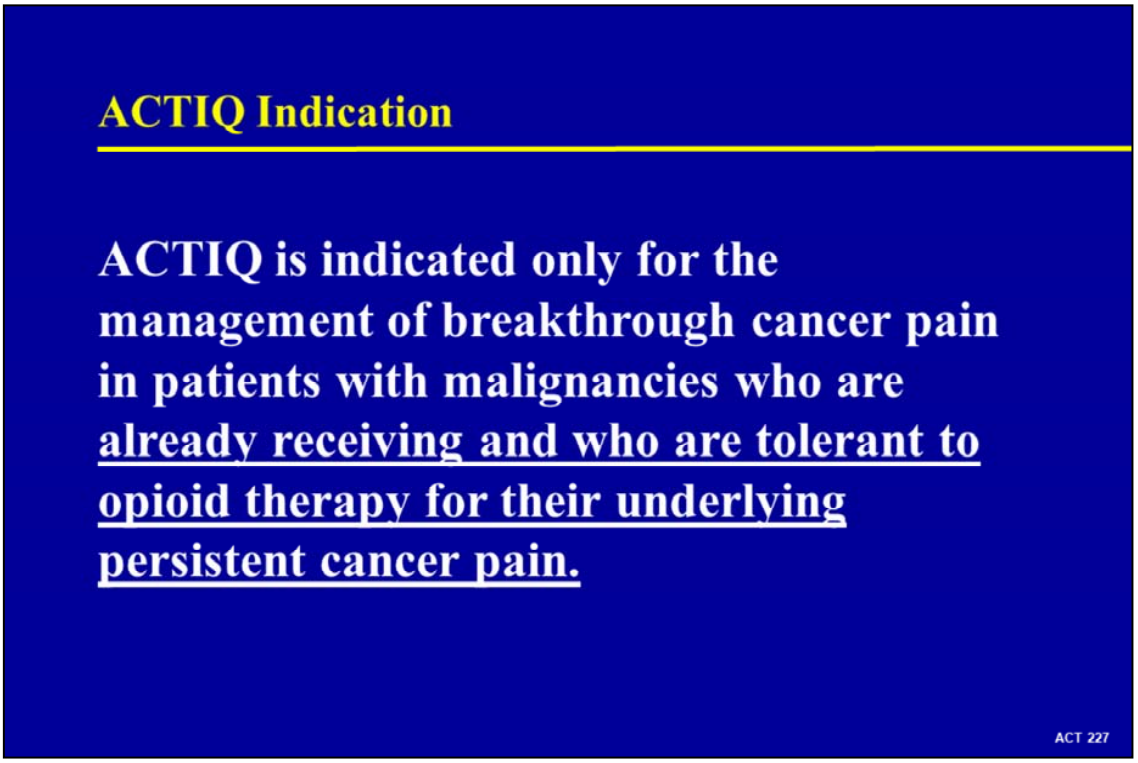


PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

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

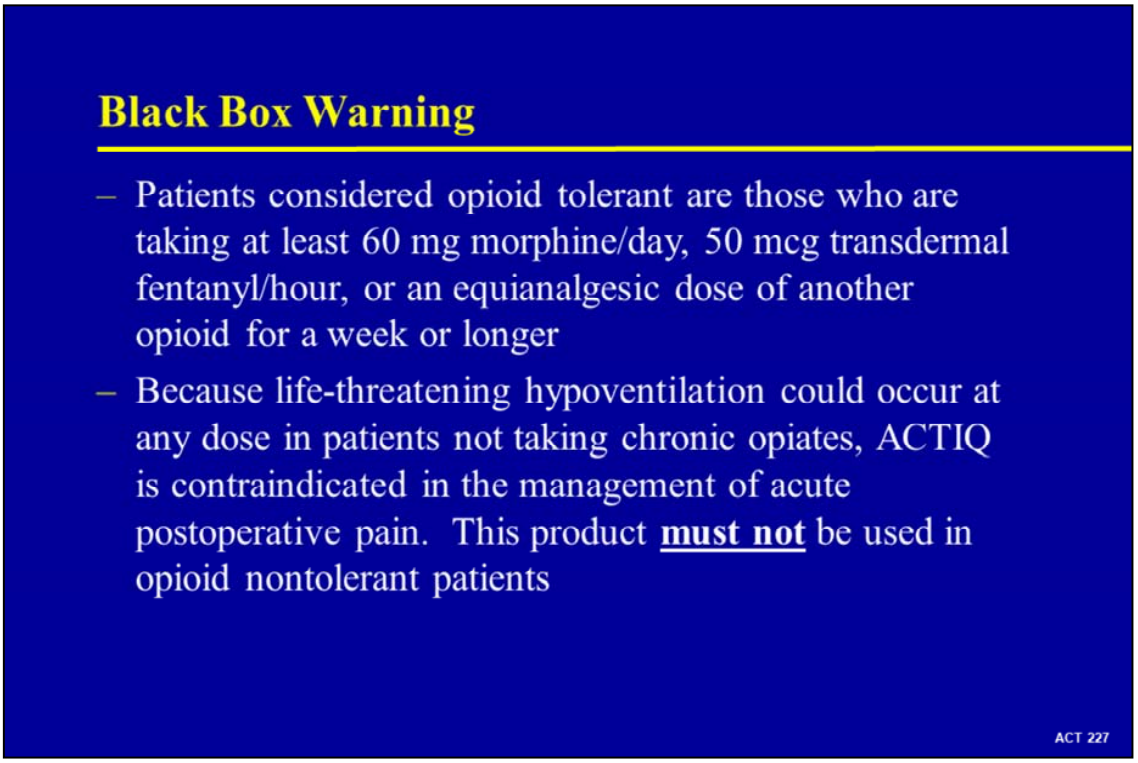
Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

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.)



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.

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.

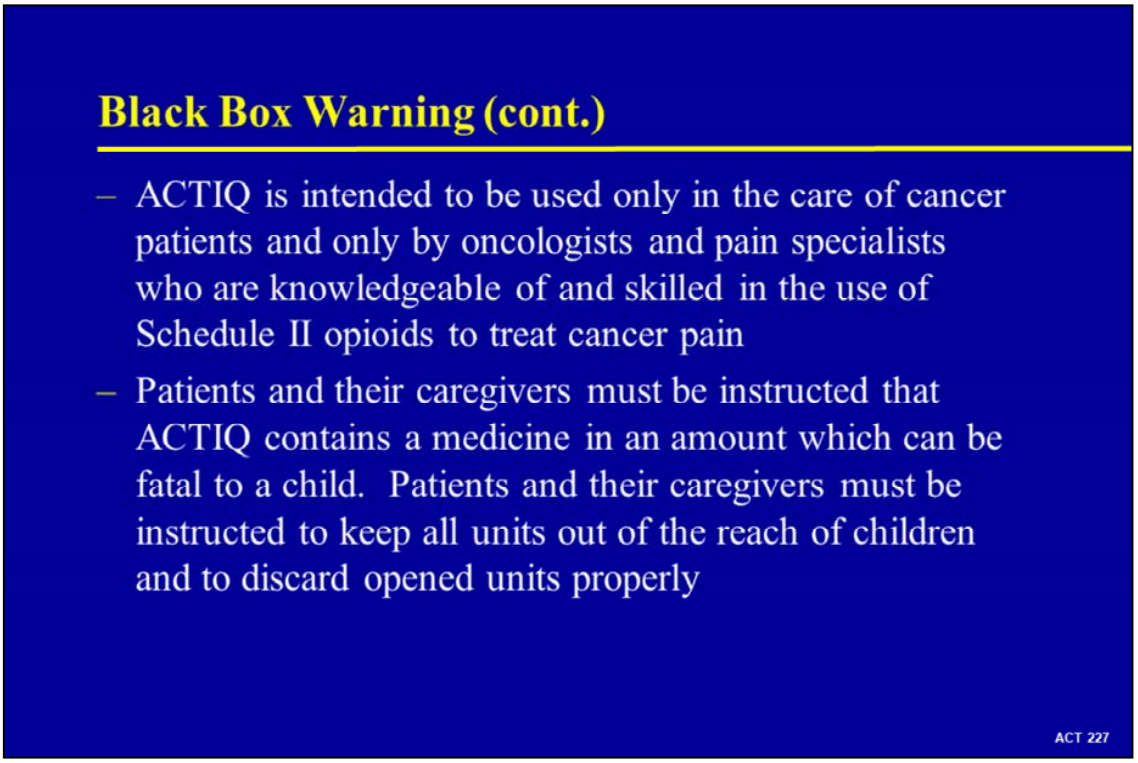


PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

***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.)

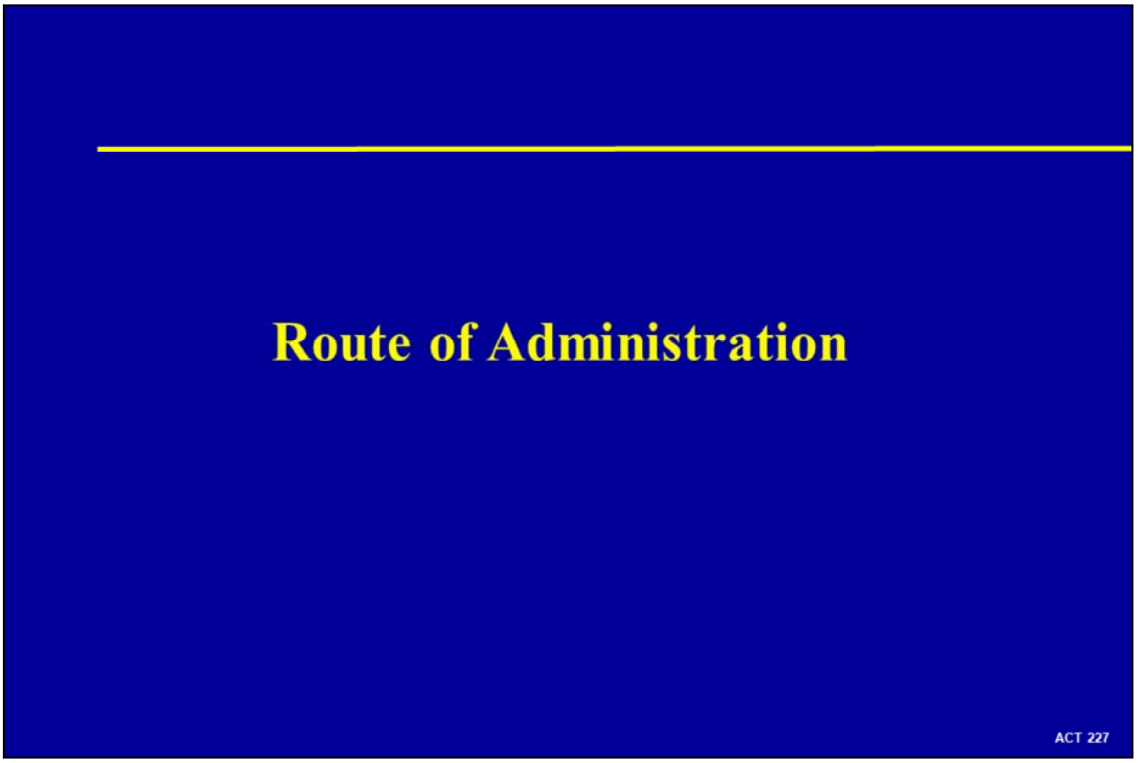


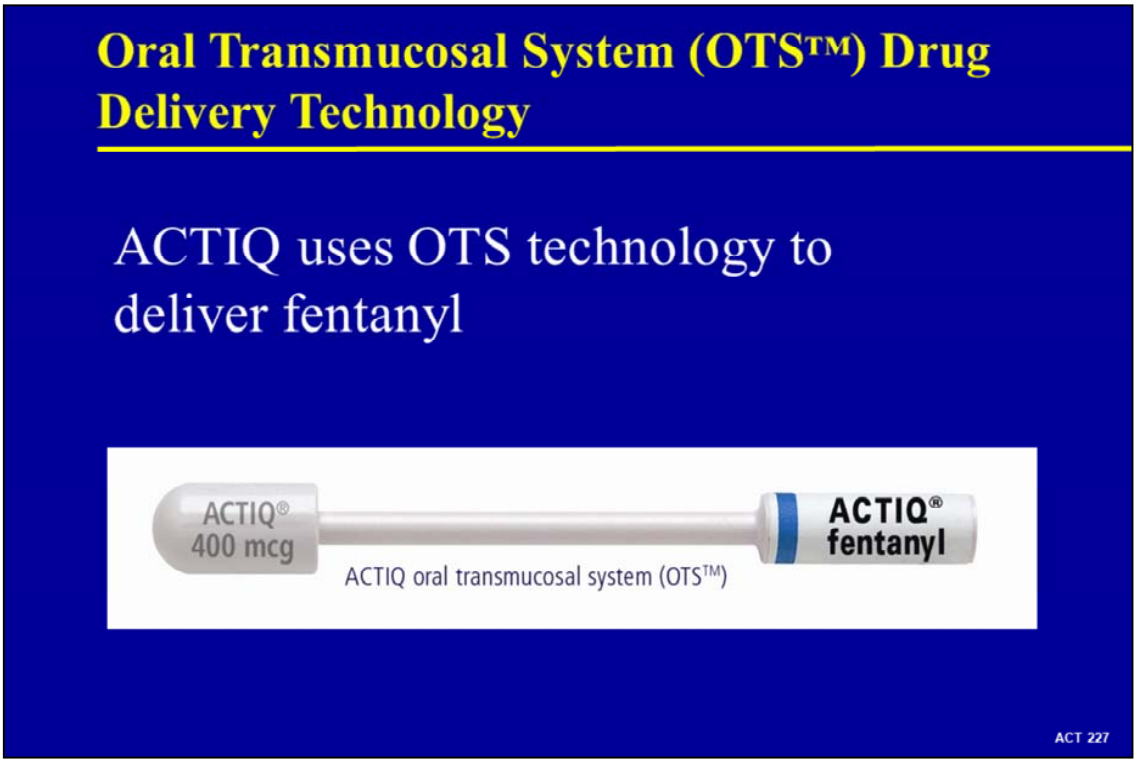
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

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.

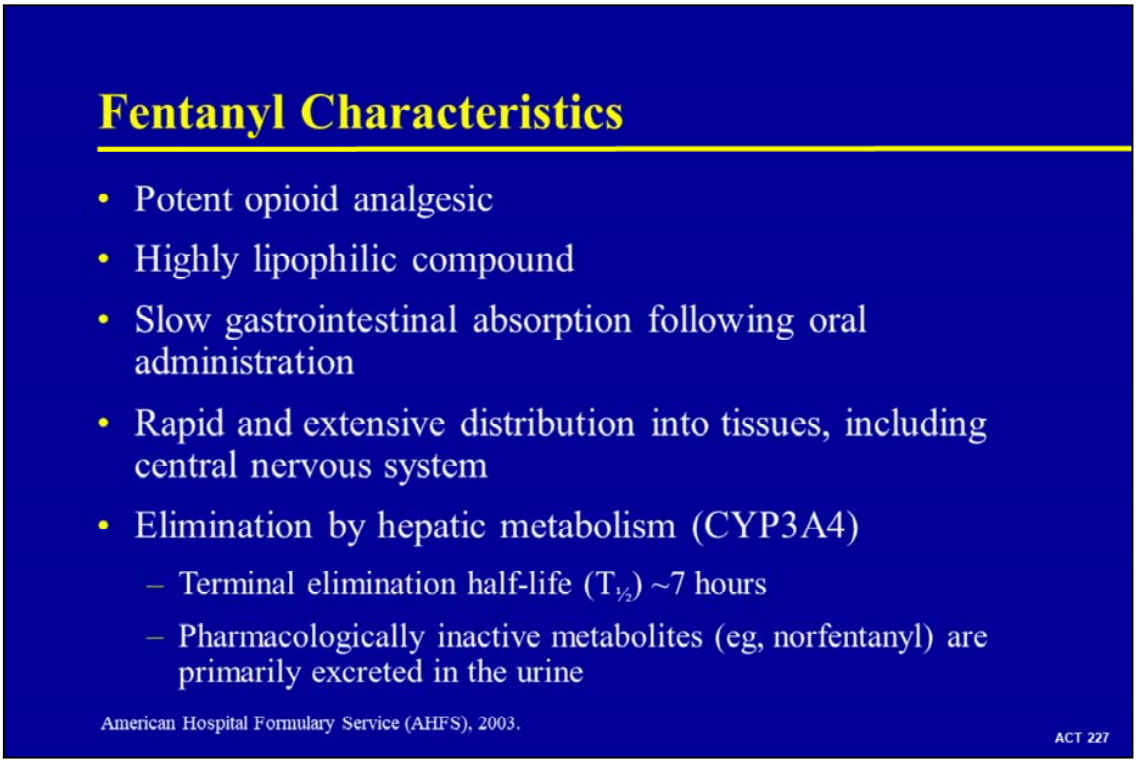
Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers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


Route of Administration
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.

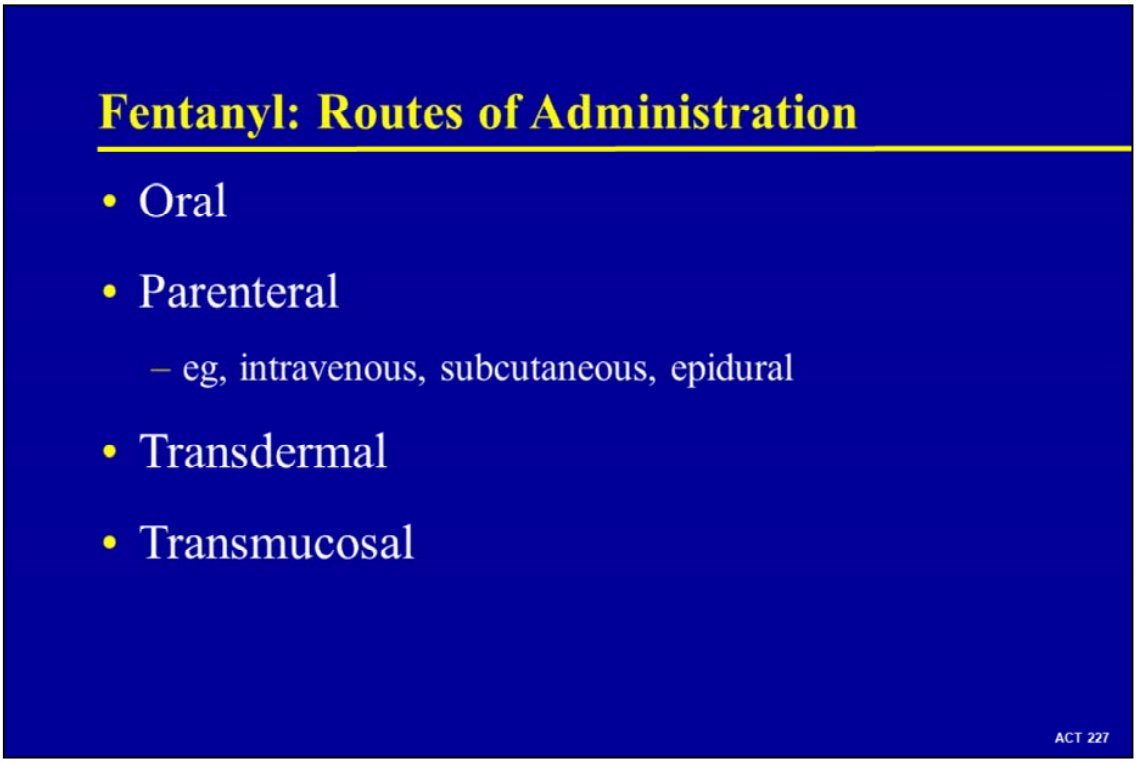


Oral transmucosal technology may be applicable to many drugs. The first drug to which the oral transmucosal technology has been applied is fentanyl citrate. It is a prime example of how oral transmucosal dosing affects drug absorption and bioavailability. Fentanyl has important pharmacokinetic properties 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.

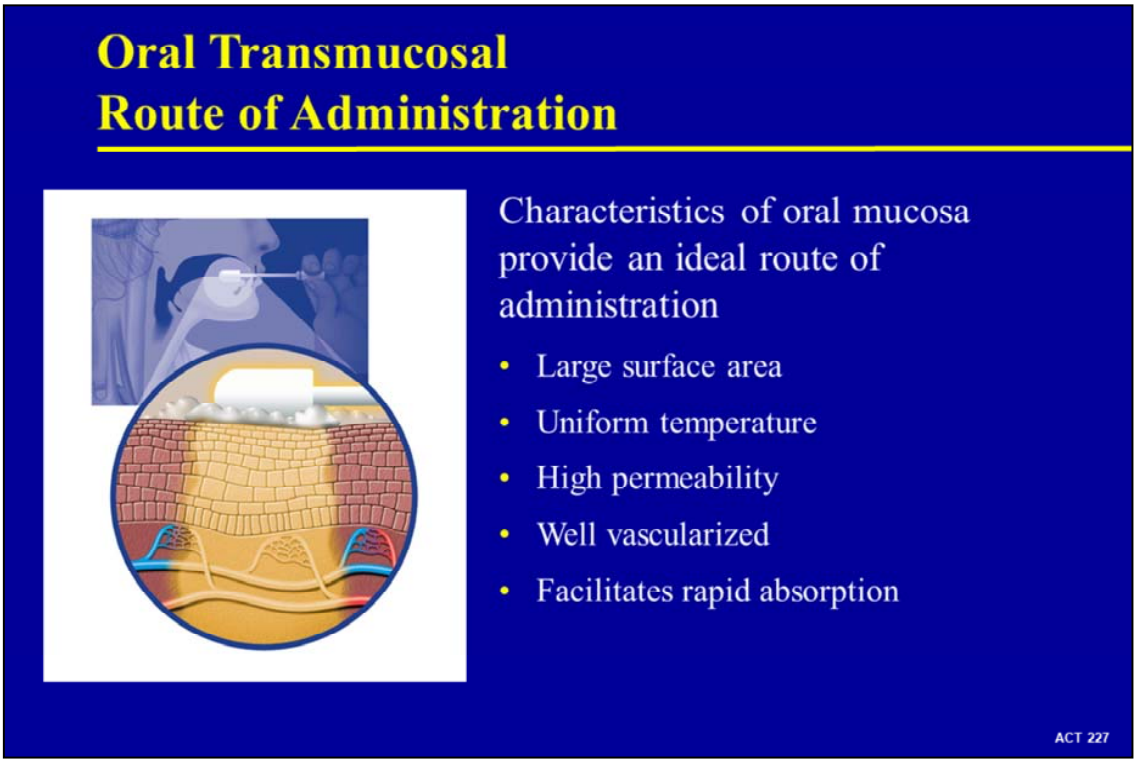
The lipophilic nature of fentanyl also allows it to be distributed widely and rapidly into tissues. When IV fentanyl was administered to normal volunteers at a dose of 15 µg/kg, the volume of distribution at steady state was much larger than the blood volume and was measured to be 287±79 L. The peak 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]



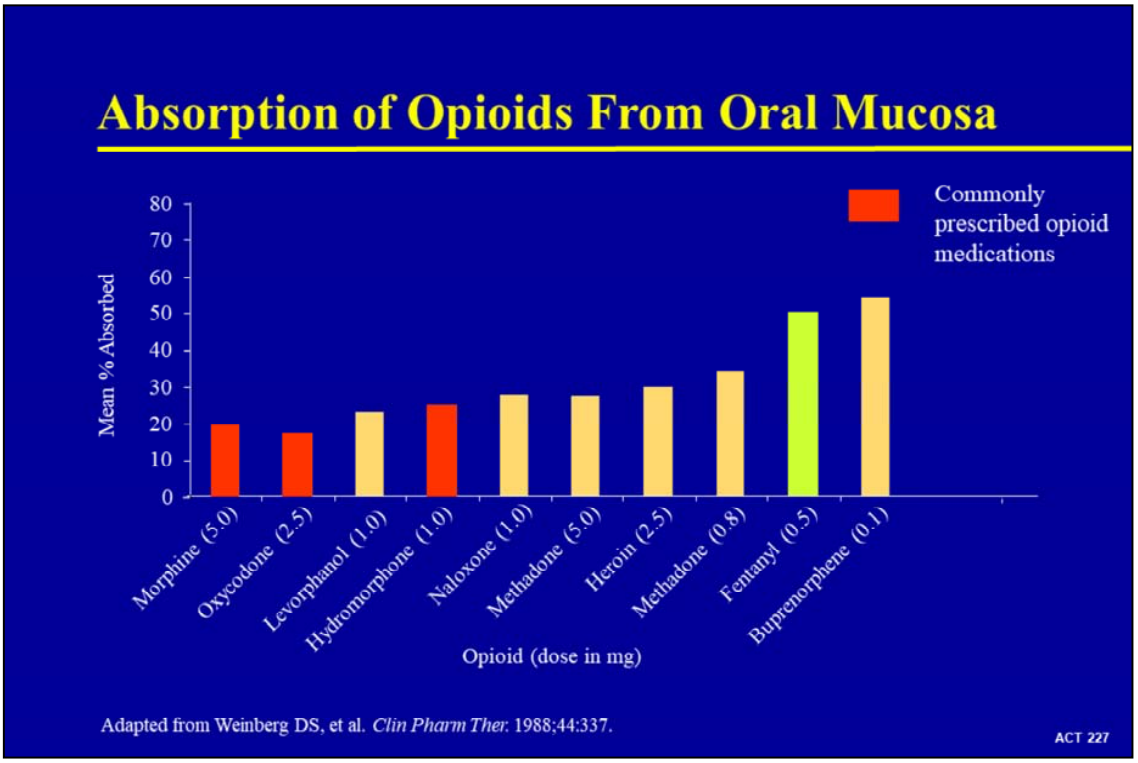
Several routes of analgesic administration are currently utilized, including oral, transdermal, transmucosal, intraspinal, rectal, intravenous and subcutaneous, nasal, or intraventricular routes. Generally, less invasive routes are preferable to more invasive ones. The oral route is one of the most convenient, 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.

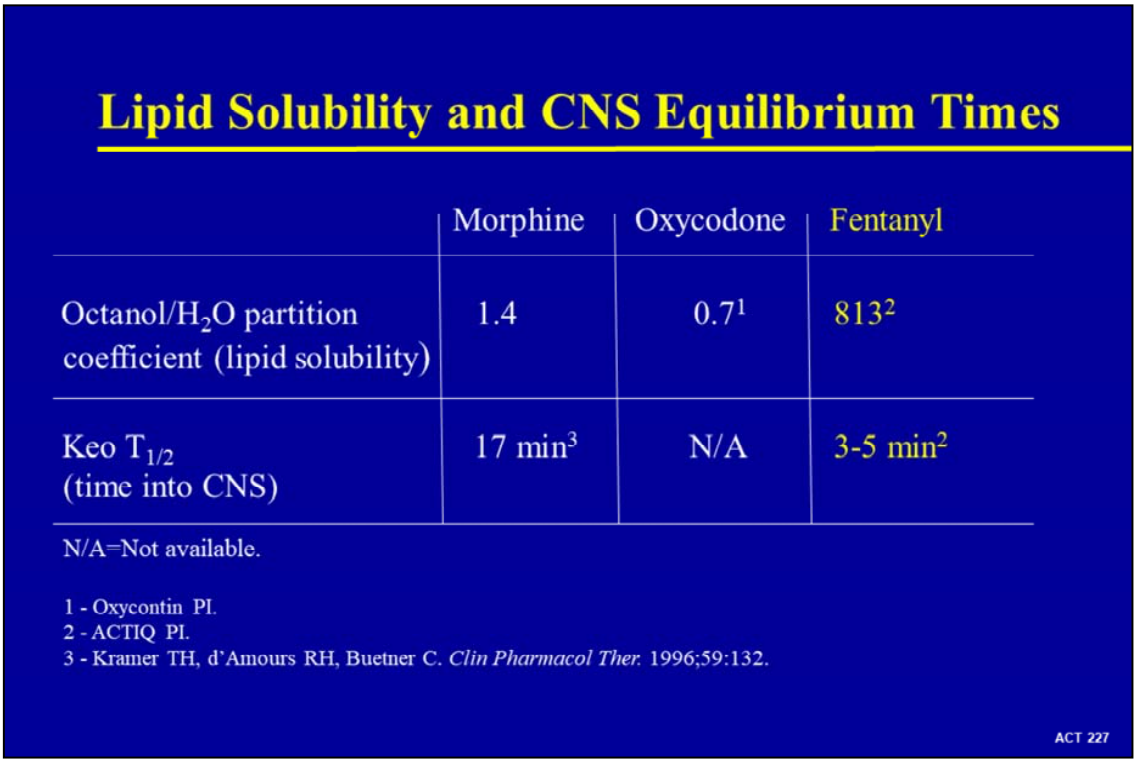


The oral transmucosal route of delivering drugs is desirable for several reasons. The oral cavity has a relatively uniform temperature and a large surface area. The oral mucosa is highly permeable — 20 times more permeable than the skin. Additionally, the oral mucosa is highly vascularized. Because of 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.

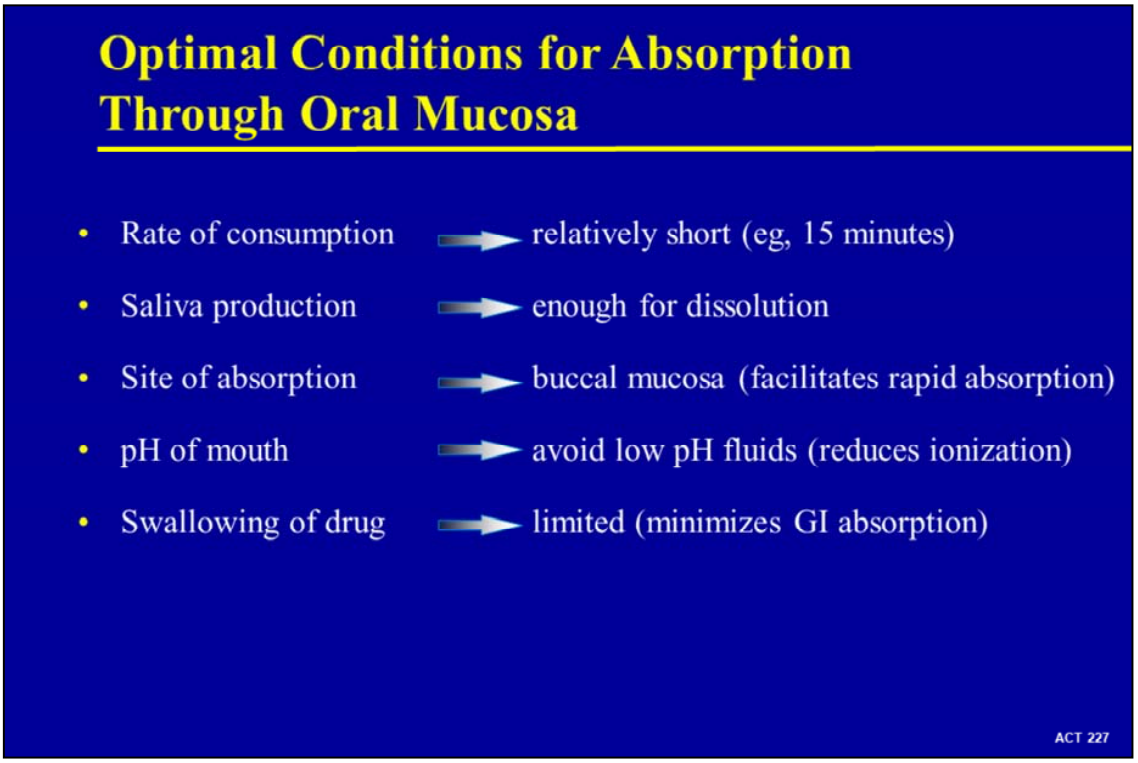
Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes 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]



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.



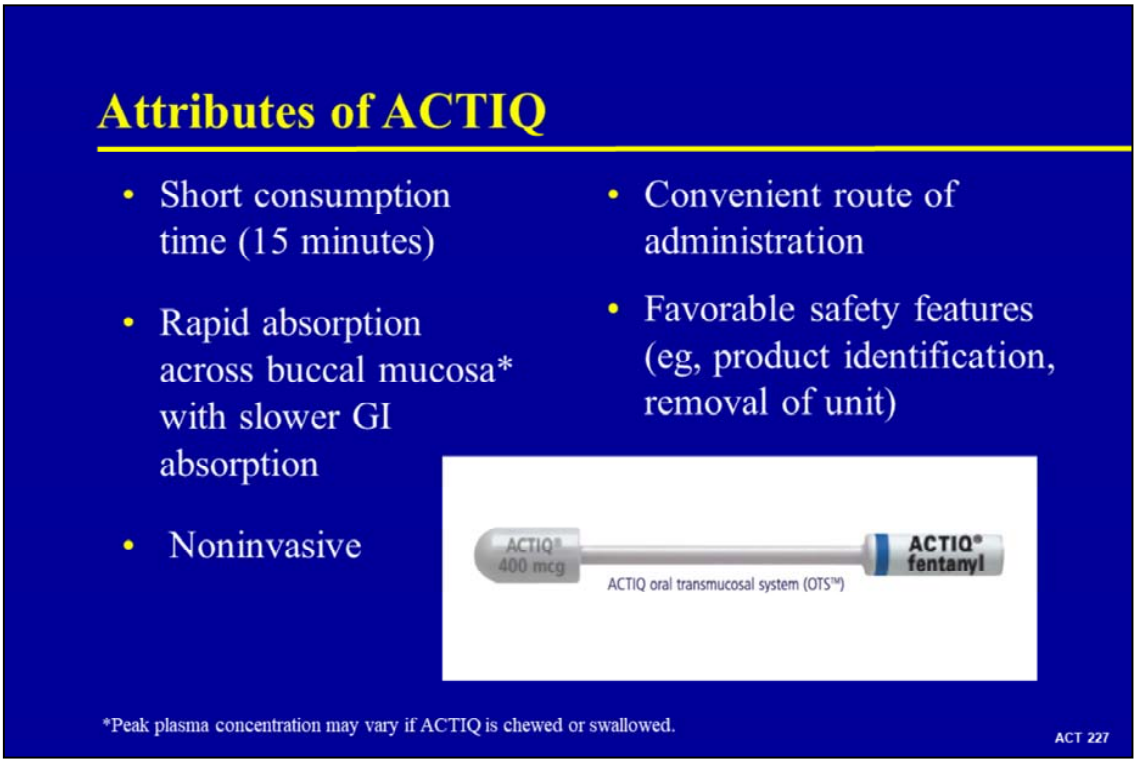
This slide reflects the lipid solubility of 3 agents: morphine, oxycodone, and fentanyl. The higher the octanol-to-water partition coefficient, the more lipid soluble it is and therefore the more readily it will cross the blood-brain barrier.



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.



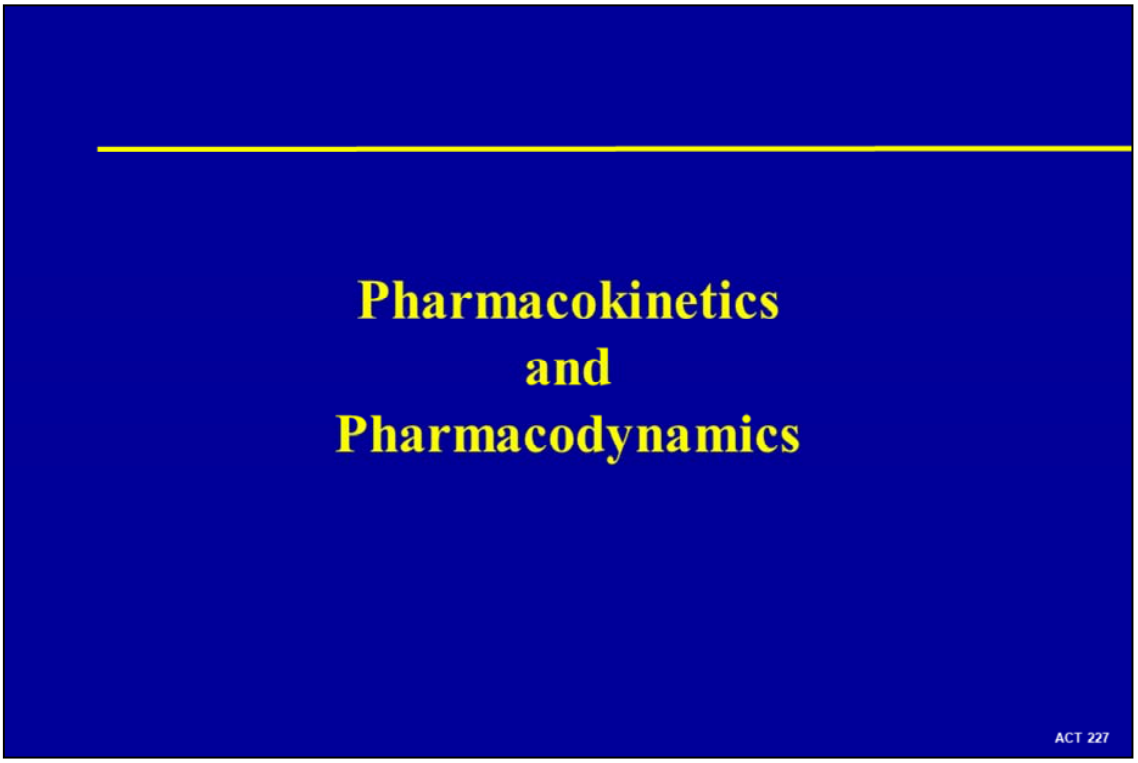
ACTIQ consists of a solid drug matrix attached to a handle. When the matrix dissolves in the patient's mouth, the drug becomes available for rapid absorption across the oral mucosa.

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.

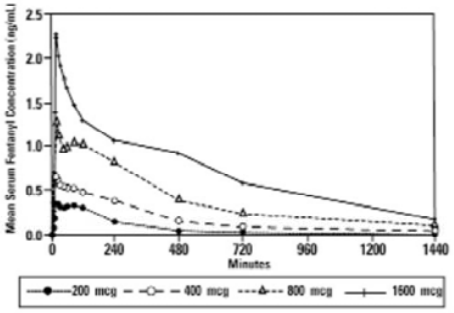
With ACTIQ, pain relief may be observed in 15 minutes. Patients may begin experiencing pain relief while taking ACTIQ, but may not experience full relief for up to 45 minutes after finishing an ACTIQ unit.

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.


Pharmacokinetics
and
Pharmacodynamics
ACT 227

Dose Proportionality Study – Fentanyl Concentration-Time Profile

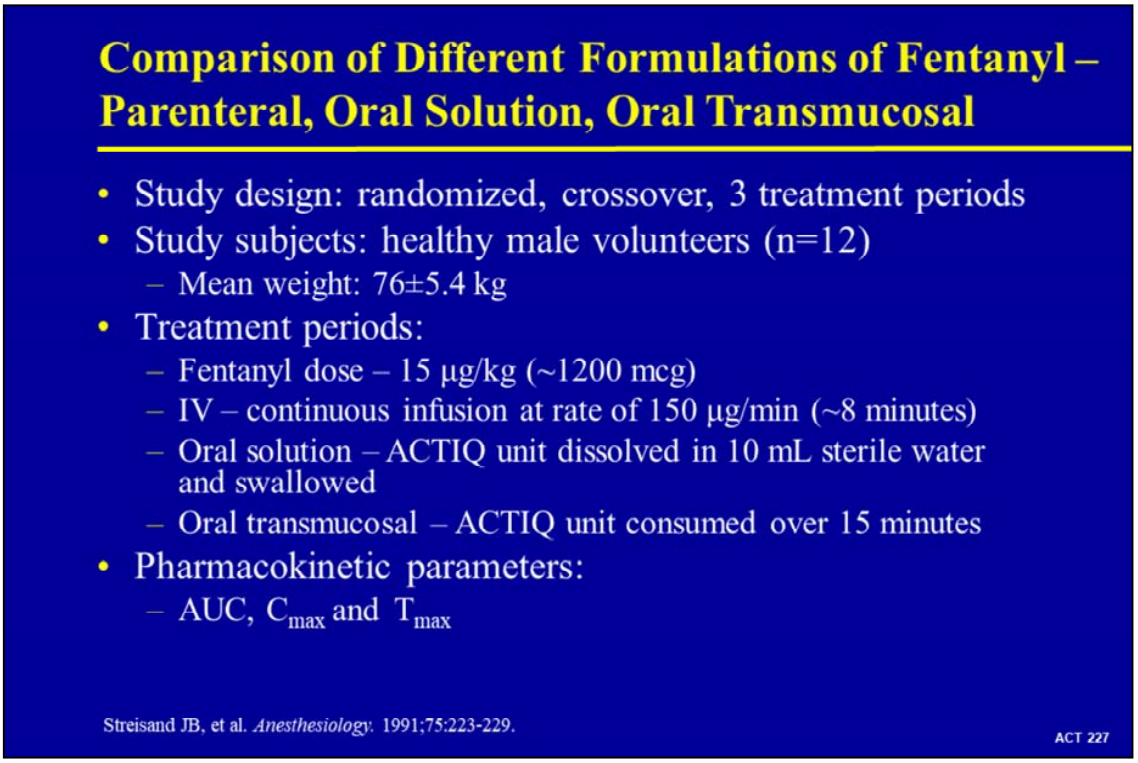
Figure 1.
Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of Actiq



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

ACT 227

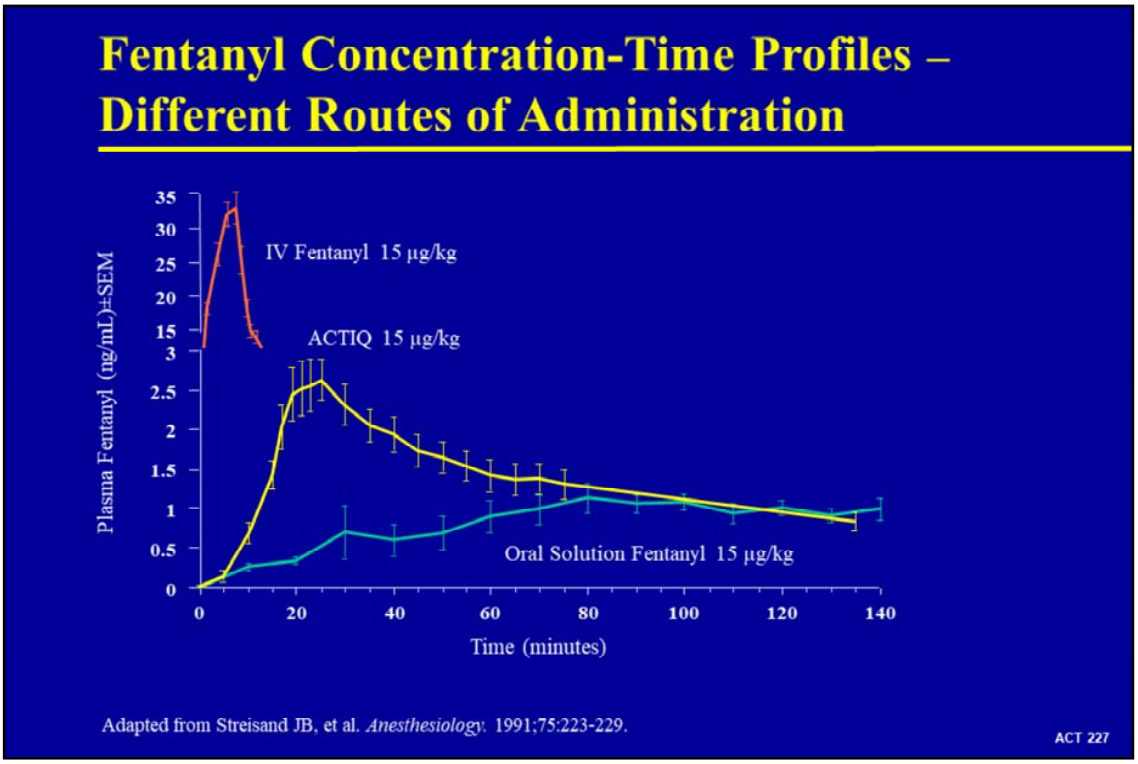
Dose proportionality among 4 of the available strengths of ACTIQ (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels following these 4 doses of ACTIQ are shown above. The curves for each strength level are similar in shape with 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.



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.

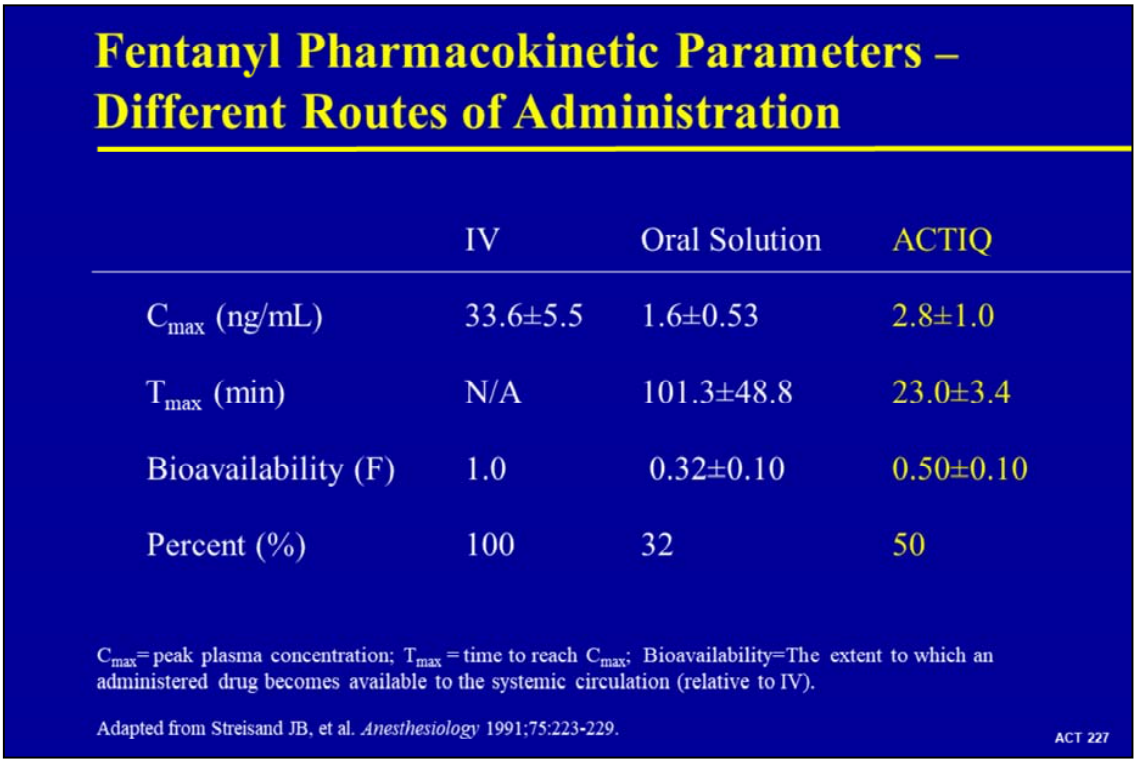


Adult male volunteers were administered 15 µg/kg of fentanyl on 3 separate days, using 3 different routes of administration: IV, oral transmucosal, and oral solution. This graph compares the pharmacokinetics of the 3 delivery methods.[11]

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]

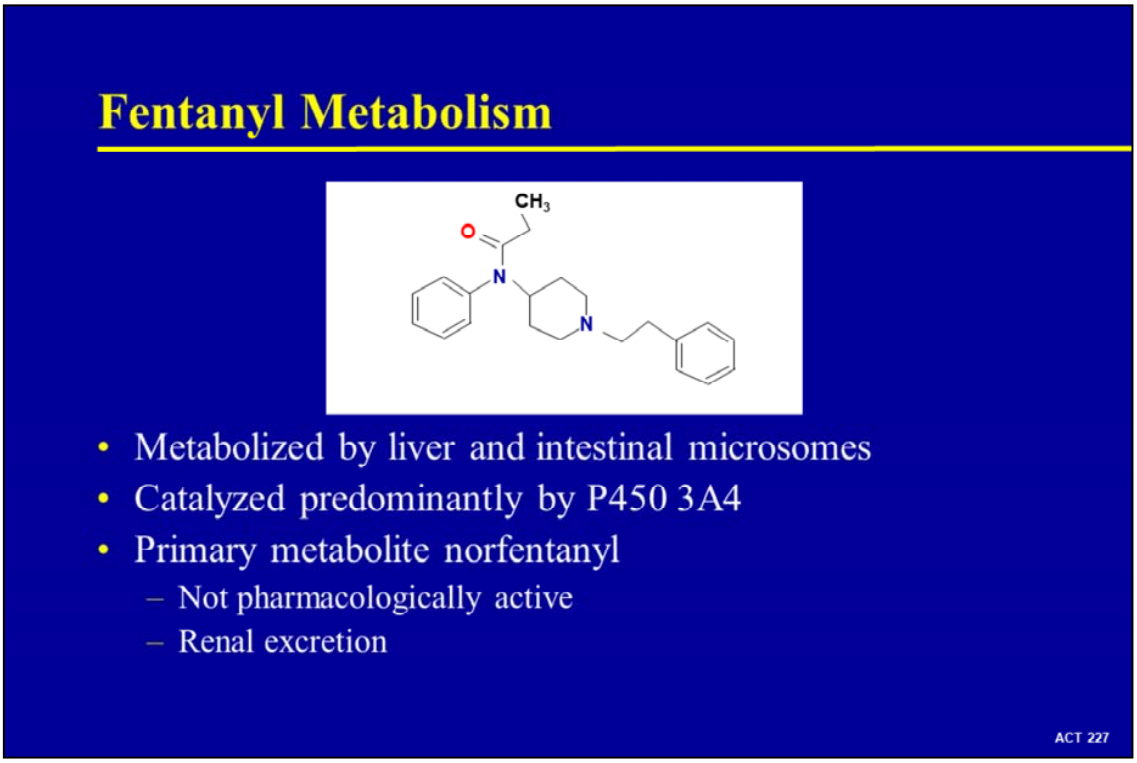
Oral transmucosal delivery provides a peak fentanyl blood level significantly faster than a swallowed oral solution (P=0.003).[11] The pharmacokinetic profile of ACTIQ approximates that of IV fentanyl in terms of time to peak blood level.

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.



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]



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.

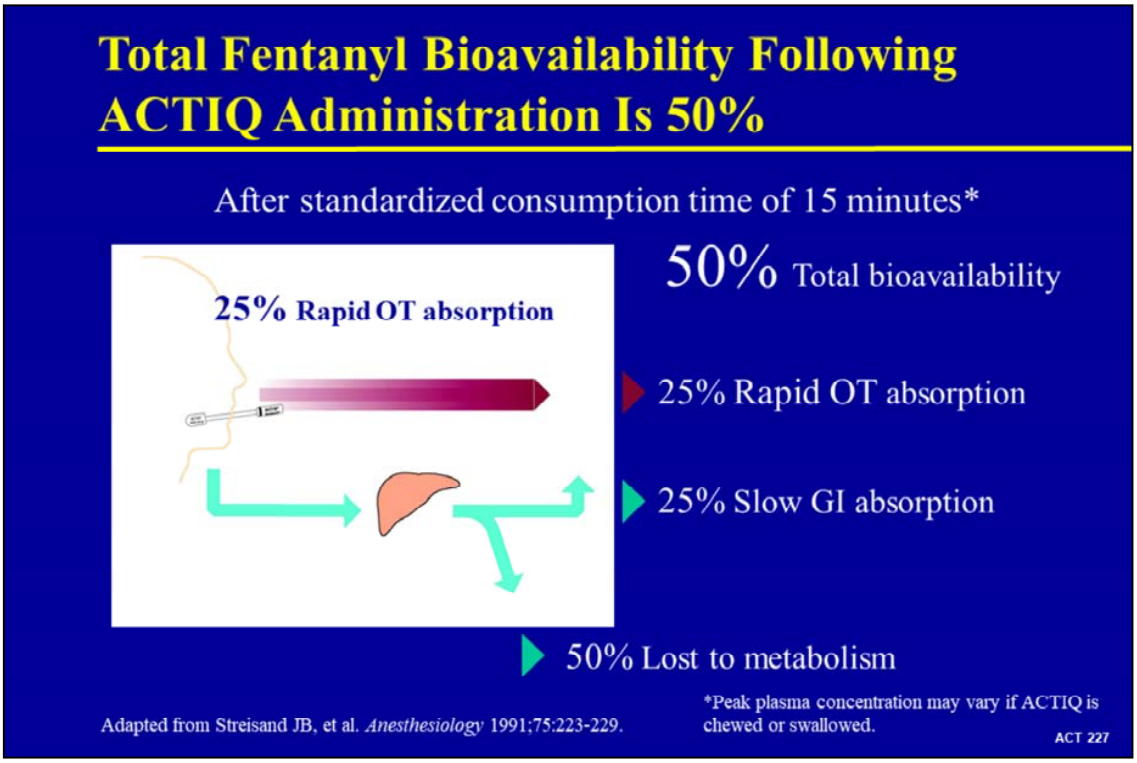
There are several clinical implications relevant to ACTIQ from these findings. Microsome enzyme activity may vary depending on interindividual variability in hepatic P450 3A4 expression and to drug interactions involving P450 3A4. There may be fast and slow metabolizers of fentanyl, and changes in other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

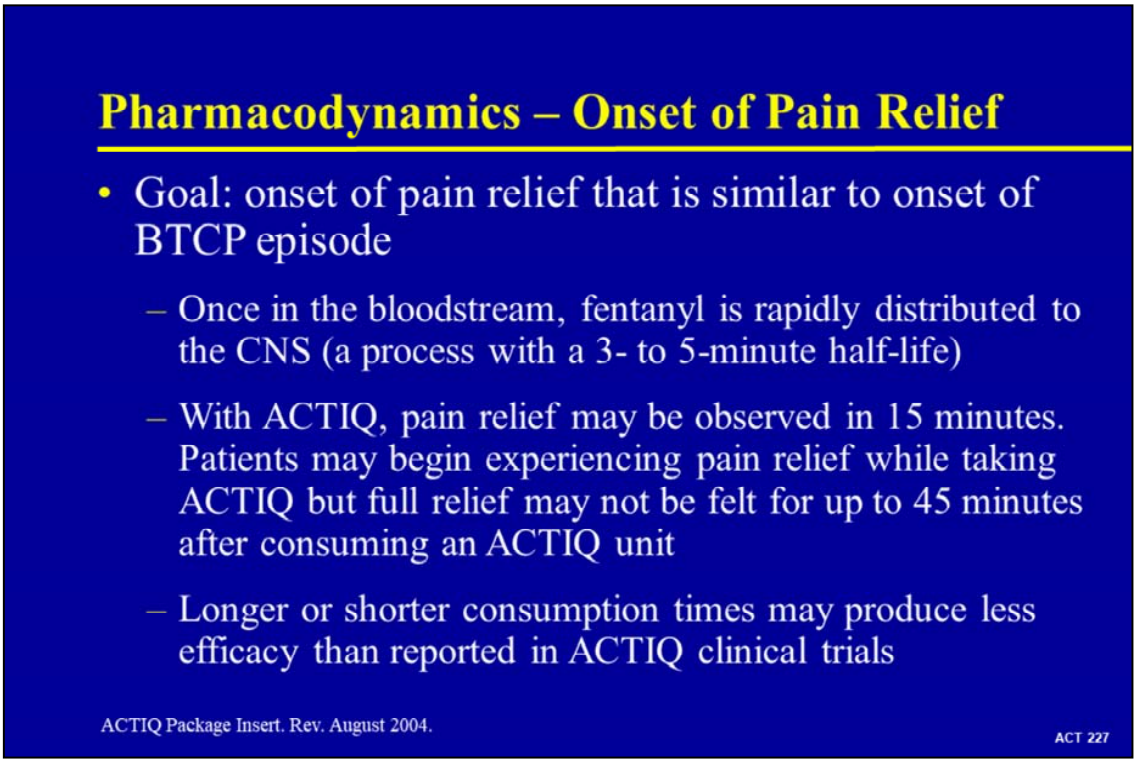
A large number of clinically important drugs act as substrates of the cytochrome P450 3A4 subfamily of metabolic enzymes. The cytochrome P450 3A4 isoform is possibly the most clinically important cytochrome P450 enzyme, comprising as much as 60% of the total cytochrome P450 content of the liver.[16]

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]



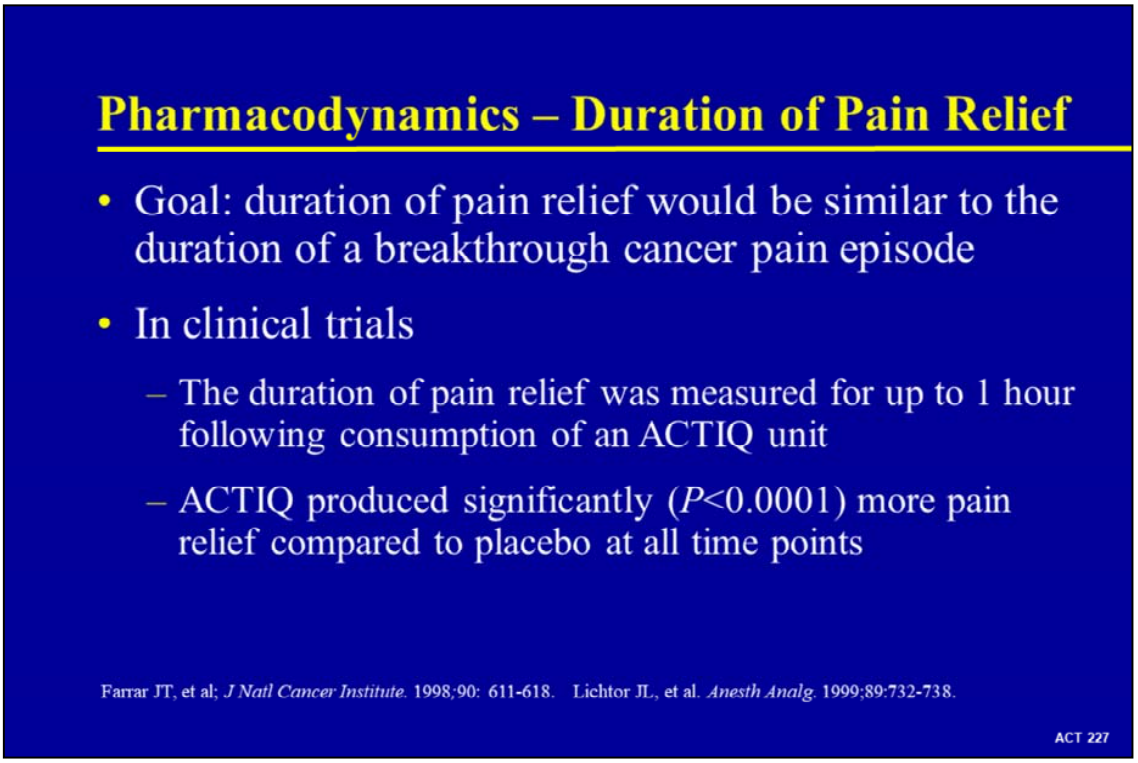
Normally, approximately 25% of the total dose of ACTIQ is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes 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.



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.

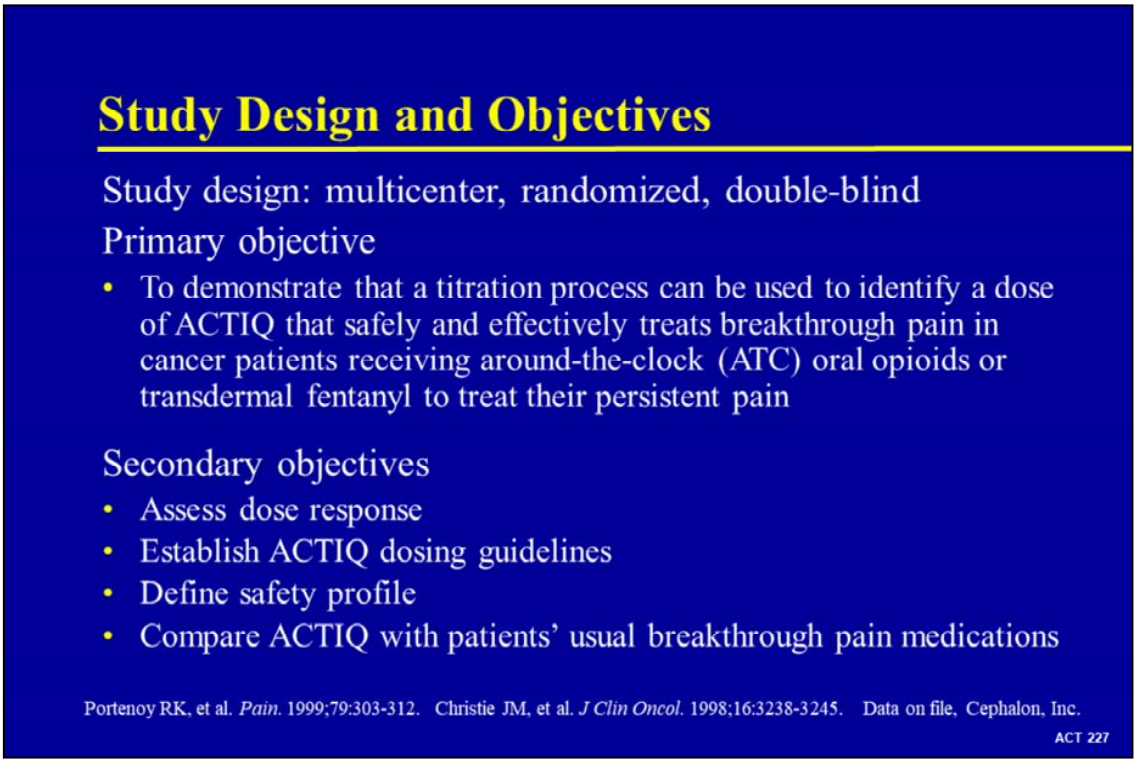
Patients should not bite or chew ACTIQ.



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



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

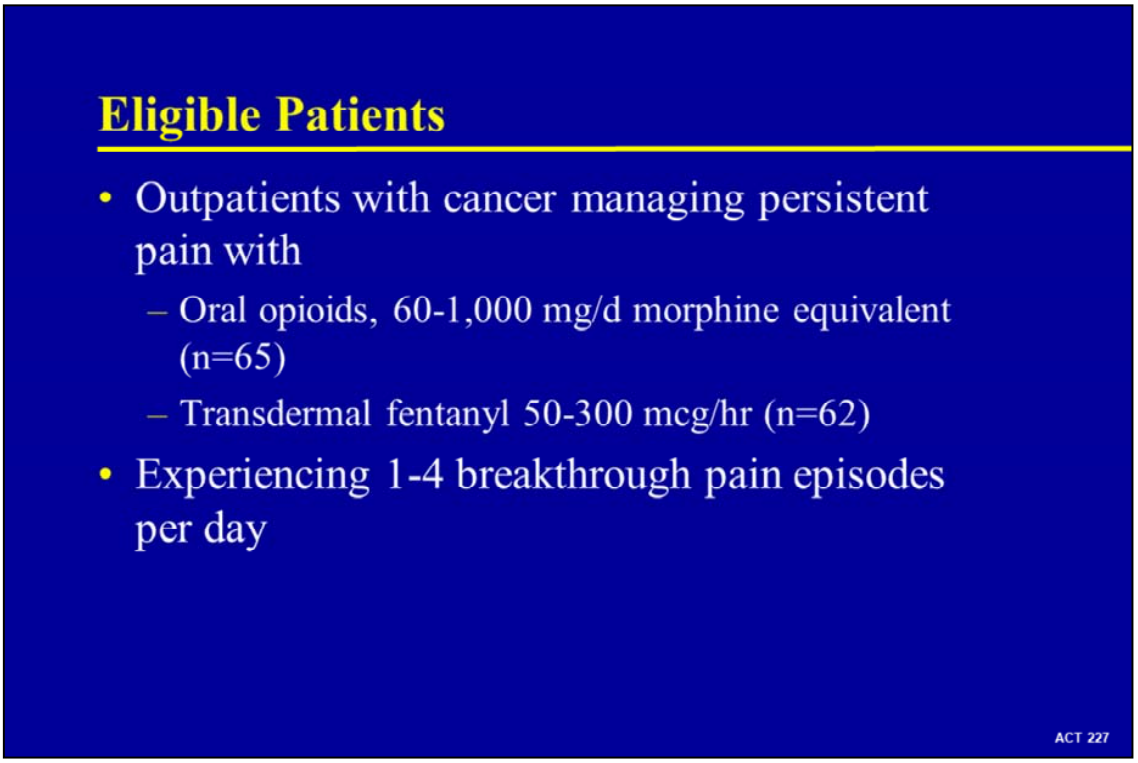
Primary Objective

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.

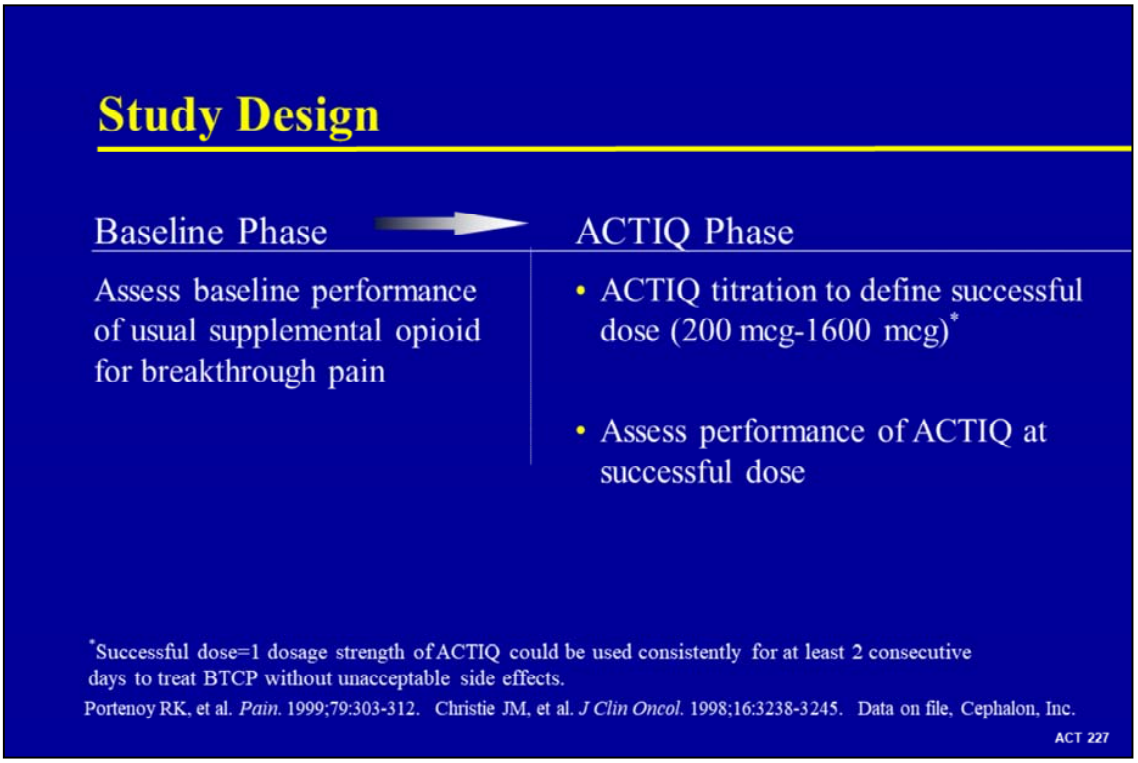


Sixty-five patients managing their ATC pain with oral opioids entered the oral study. The mean morphine equivalent dose range for these patients was 60-1000 mg/d.

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.



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.

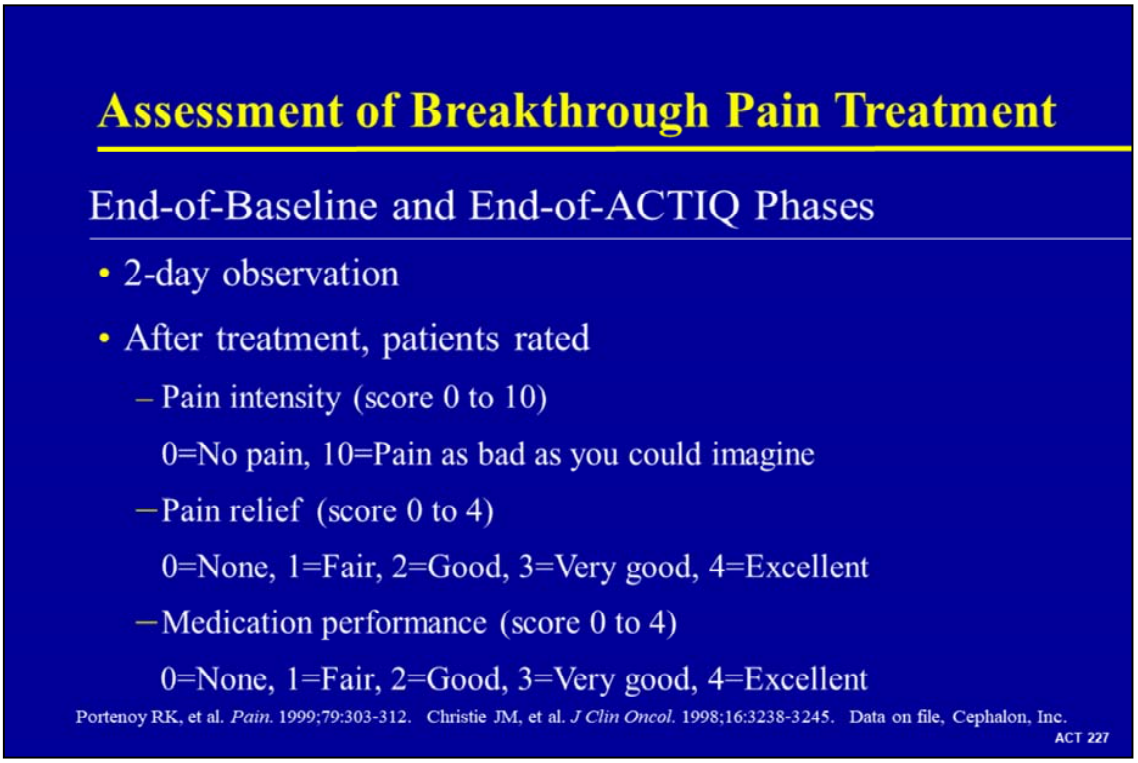
Baseline Phase

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

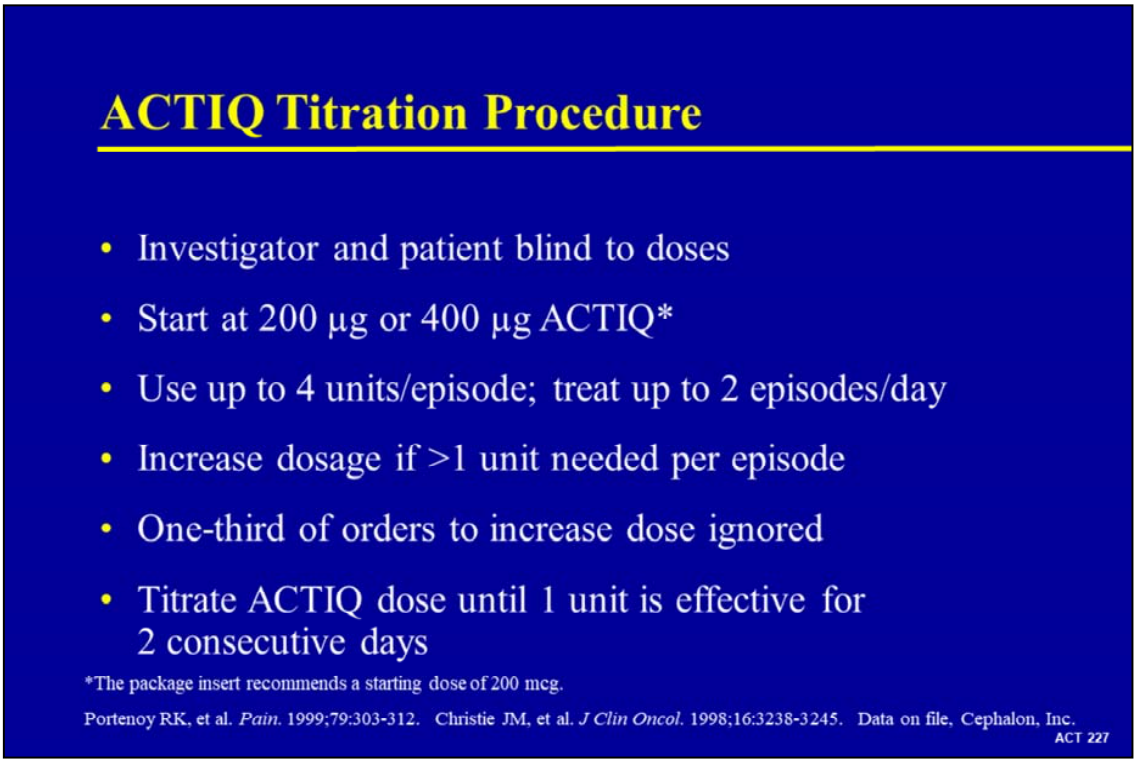
Baseline data concerning the performance of the patient's usual breakthrough pain medication was collected on 2 consecutive days during a period of stable dosing. "Stable dosing" was defined as at least 3 consecutive days during which the scheduled opioid regimen yielded an average daily pain of moderate 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.



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.



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.

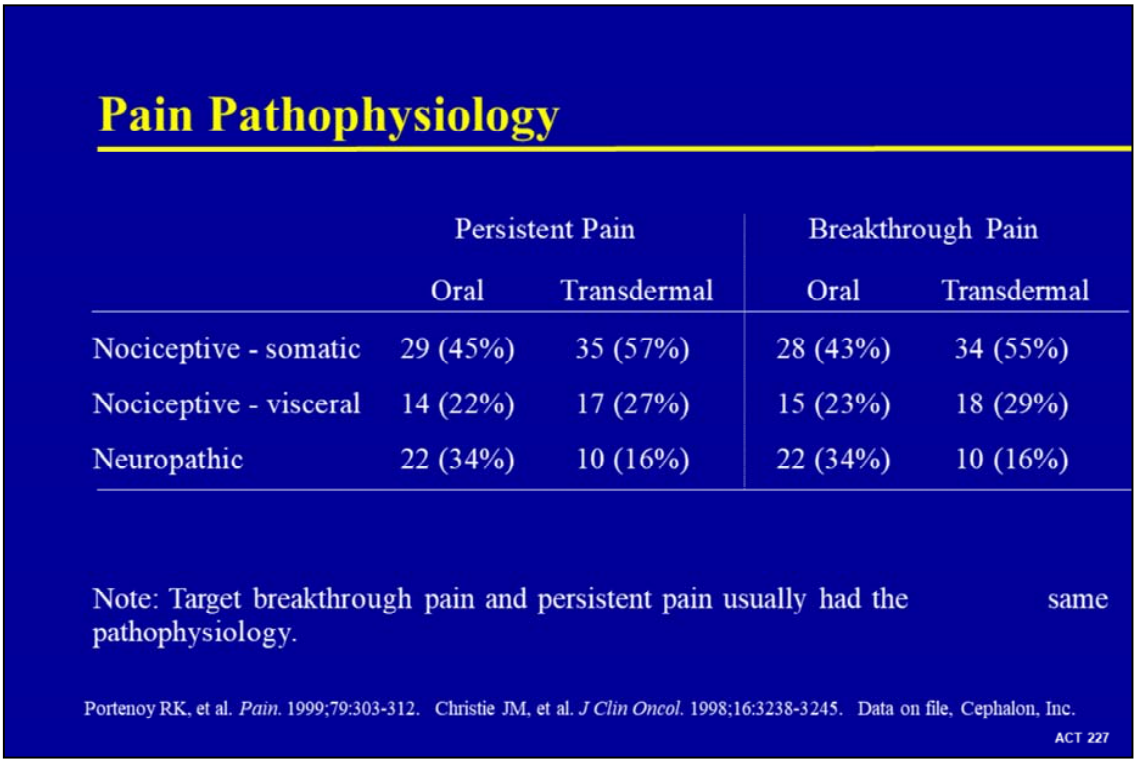
Each day, up to 2 episodes of breakthrough pain could be selected for ACTIQ treatment. The usual supplemental pain medication was used to treat all other breakthrough pains on these study days. When the patients experienced an episode of breakthrough pain, they self-administered a complete ACTIQ unit. 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.



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]

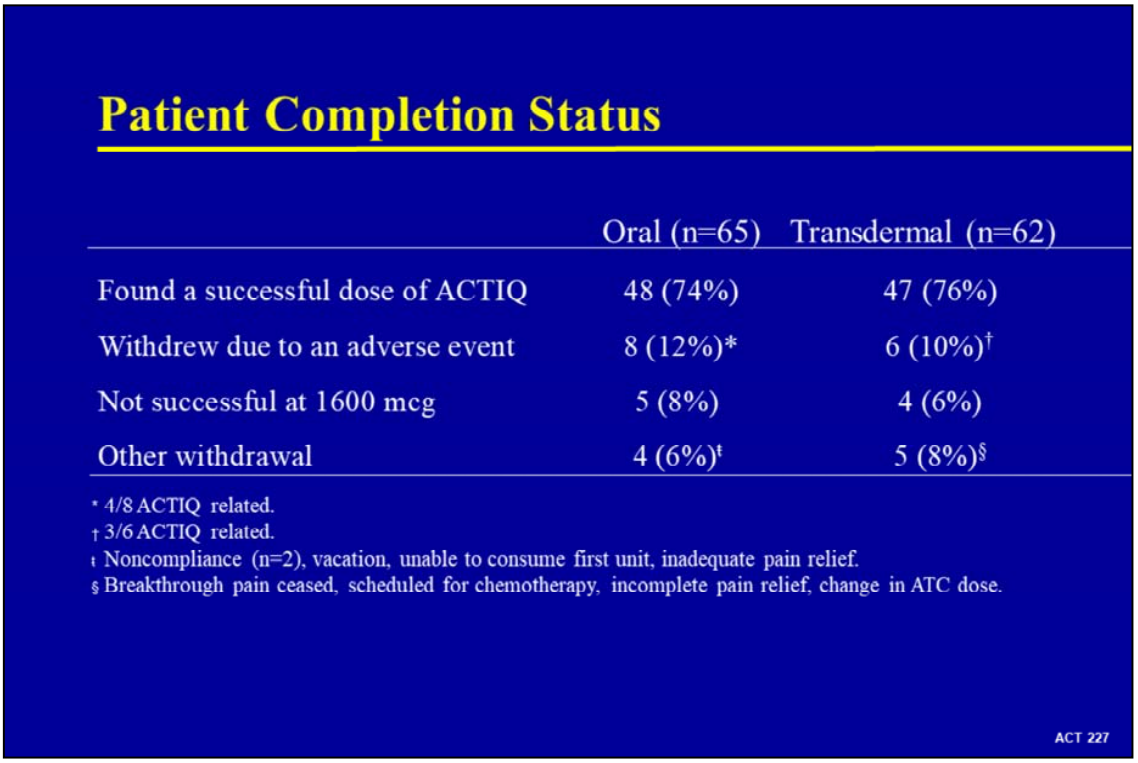
The predominant pain pathophysiology for each patient was recorded at the beginning of the study. In nearly all cases, the patient's predominant persistent and breakthrough pain were of the same pathophysiology, suggesting that the patient's breakthrough pain was most likely an acute exacerbation of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



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.

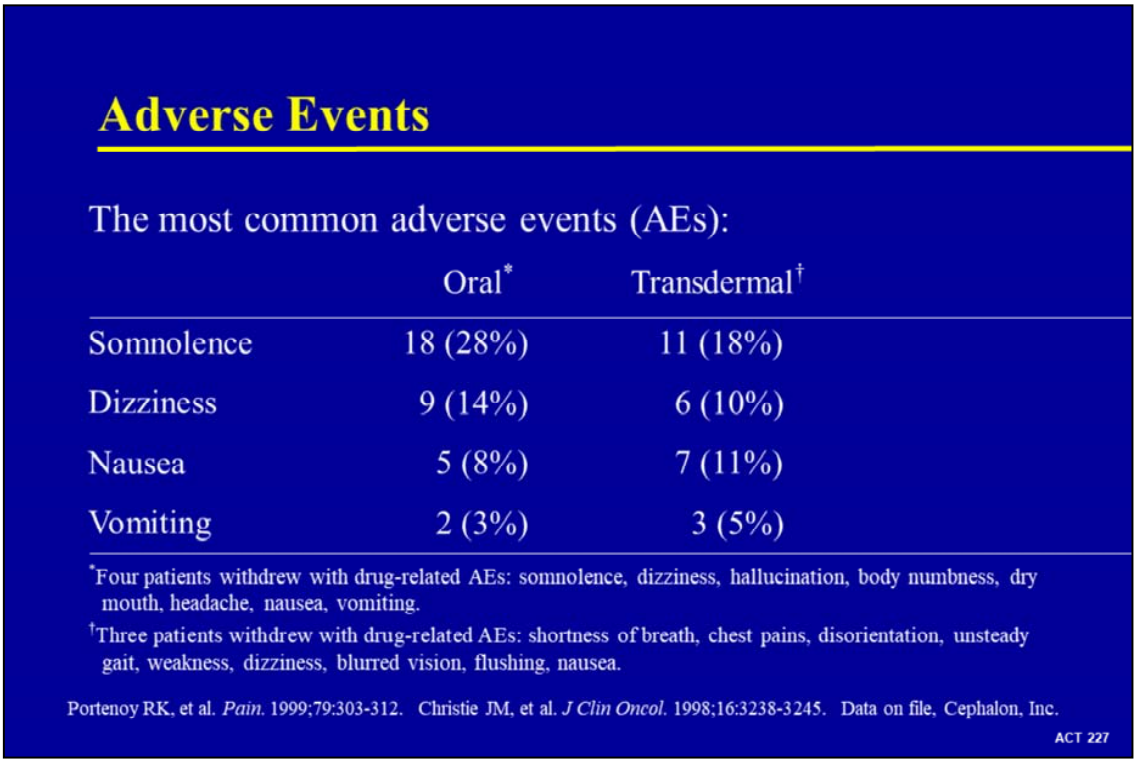
Transdermal Study

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.



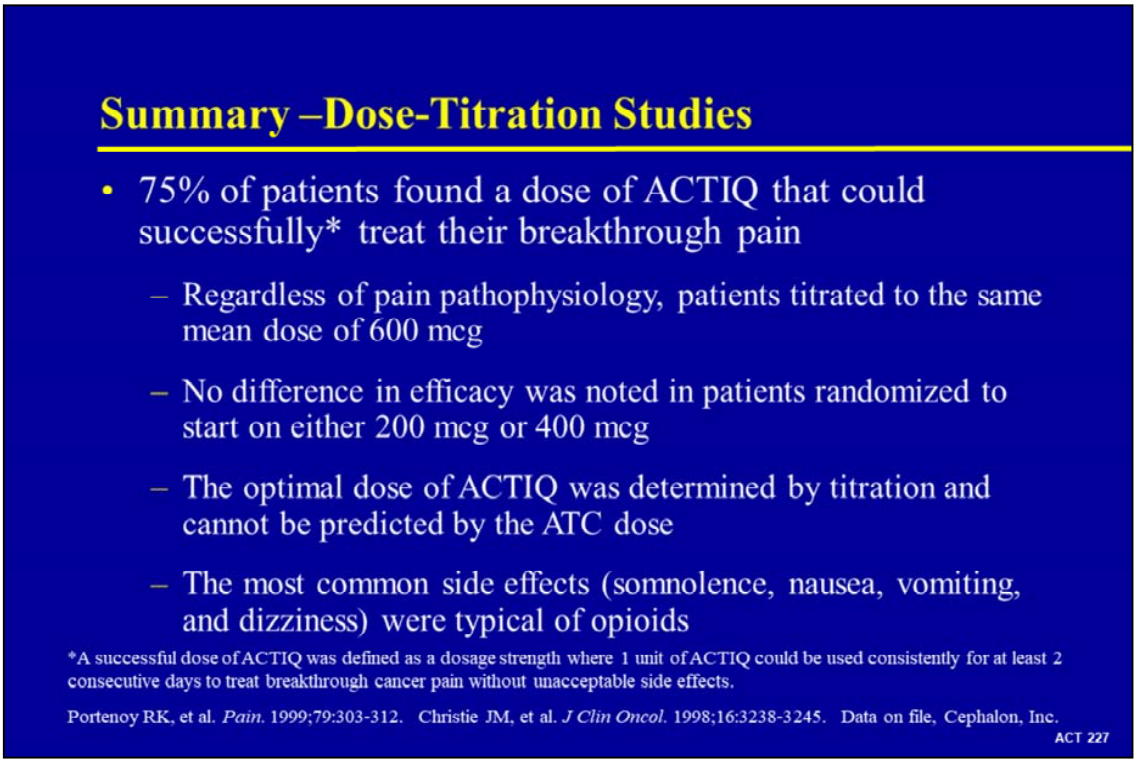
The adverse events associated with ACTIQ were typical opioid-related events. On the days that any ACTIQ was taken, adverse events that occurred with a frequency of >5% and were considered by the investigator to be possibly, probably, or almost certainly associated with the study drug. The events were 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.



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

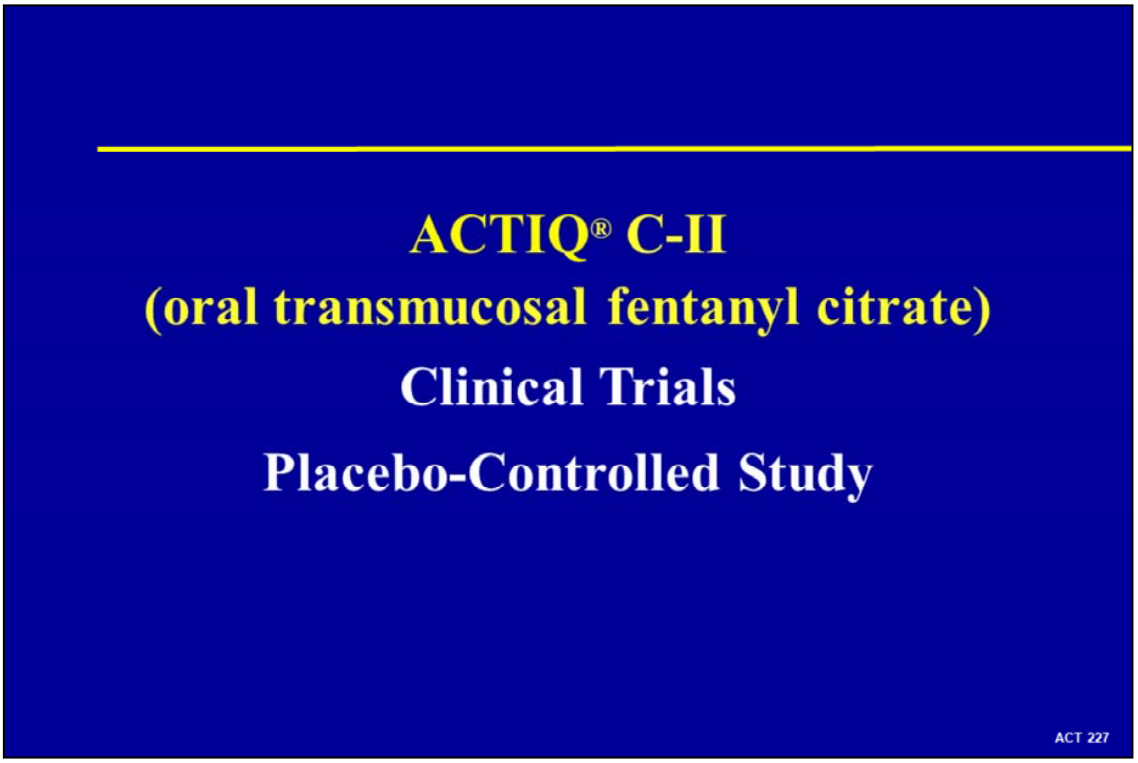
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

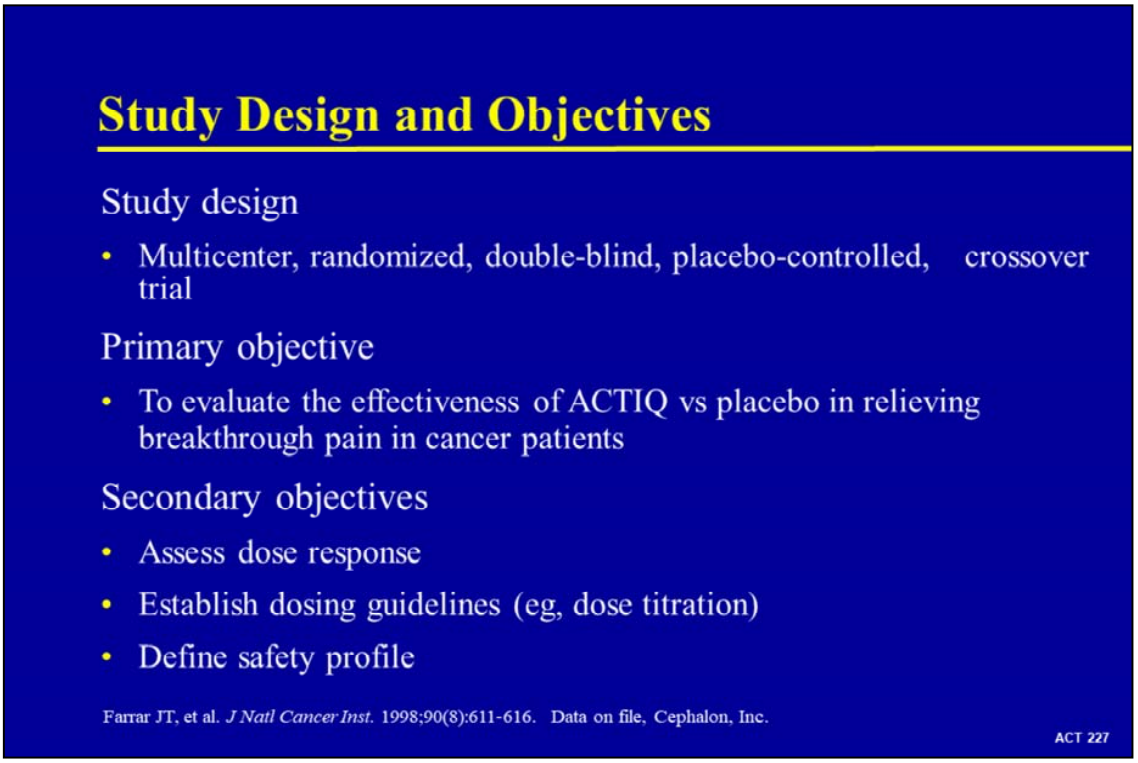
The most serious adverse effects with all opioids are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.[13]

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.

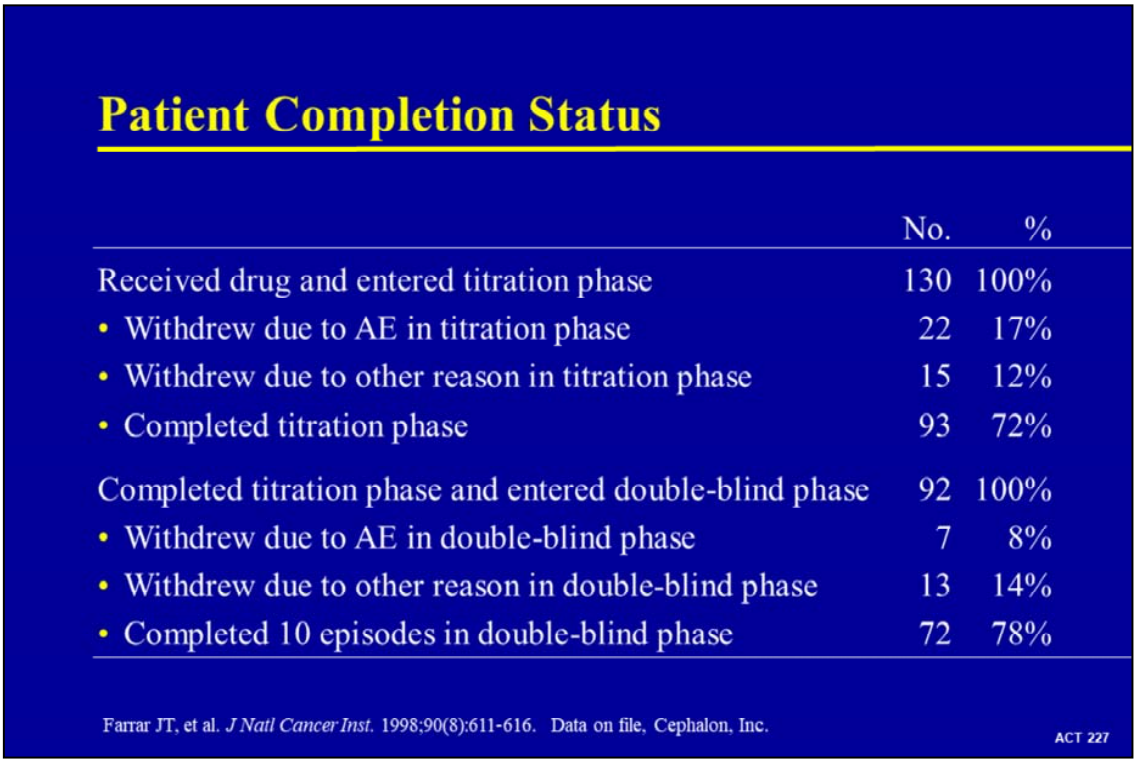

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Clinical Trials
Placebo-Controlled Study
ACT 227



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.



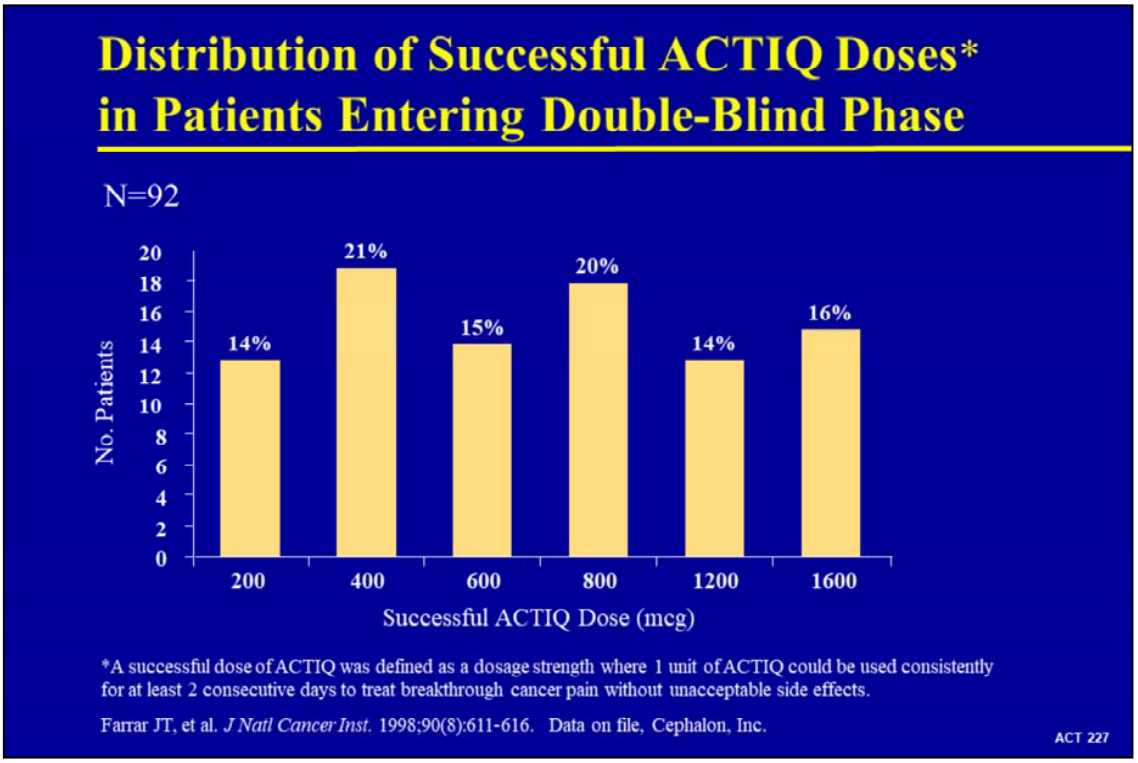
Titration Phase

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.

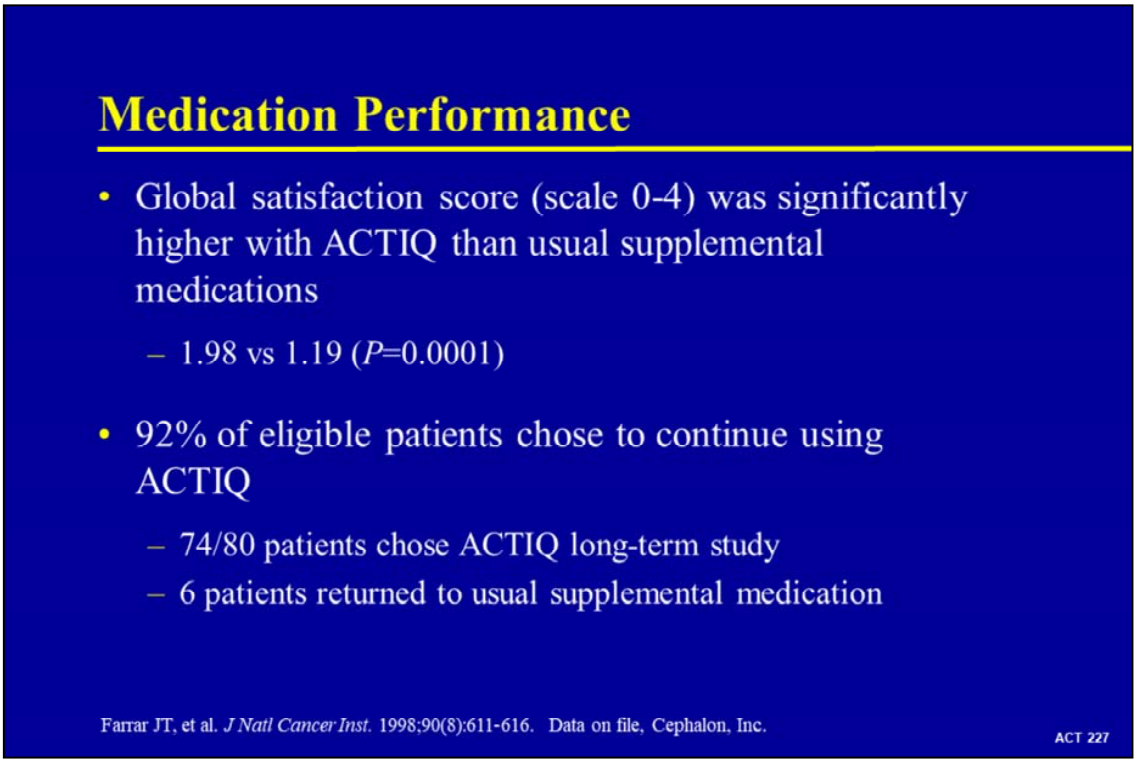


All ACTIQ dose strengths (200 mcg-1600 mcg) were used in the study. The patients' successful doses were evenly distributed among each of the unit dose strengths (percentages ranged from 14% of the patients using the 200-mcg and 1200-mcg dose strengths to 21% of the patients using the 400-mcg dose strength).

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

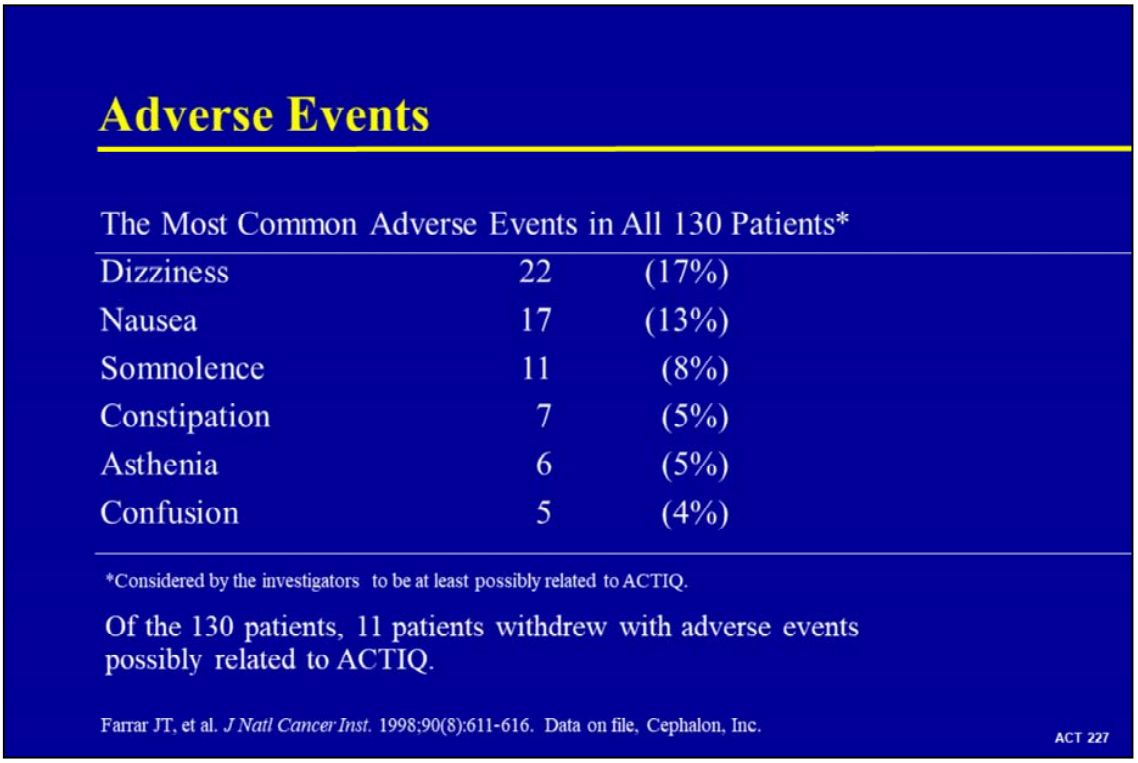
The successful dose of ACTIQ for BTCP is determined by dose titration and could not be predicted by dosage of long-acting opioid.

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.



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.



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 ≥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.

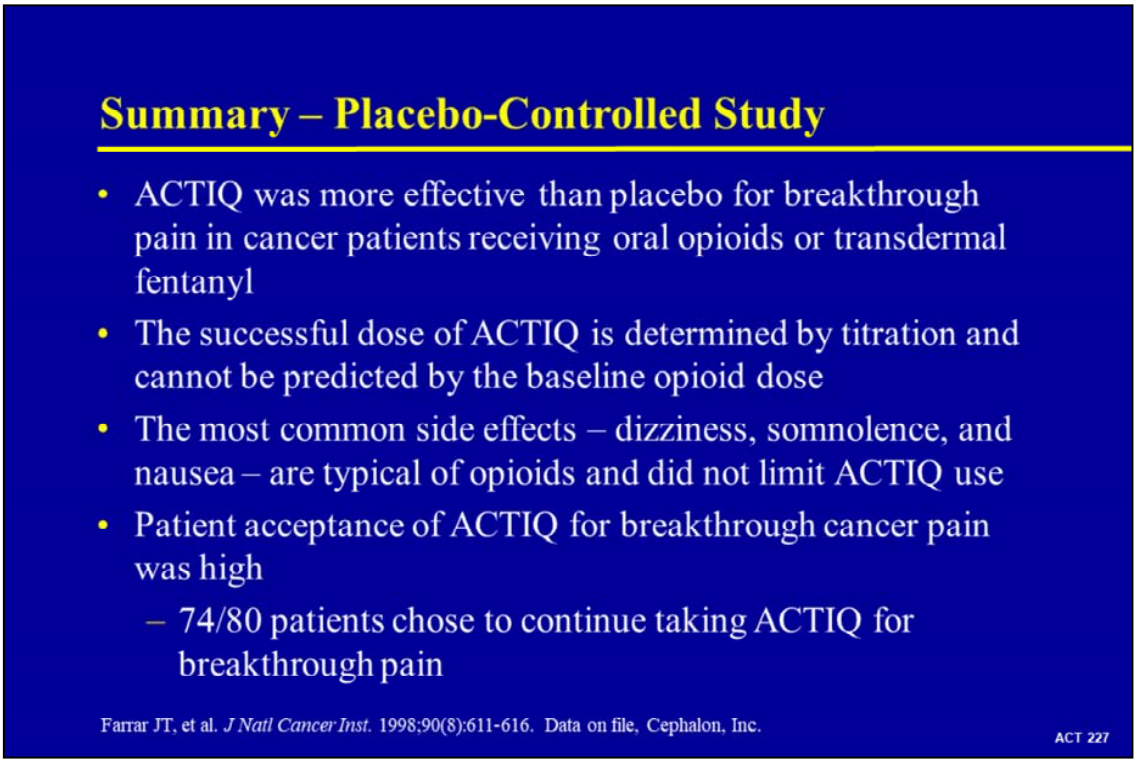
Of the 130 patients enrolled, 29 patients withdrew because of an adverse event. Eleven patients withdrew for an adverse event at least possibly related to ACTIQ. Nausea was the most common adverse event reported in the patients who withdrew from the study.

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.



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

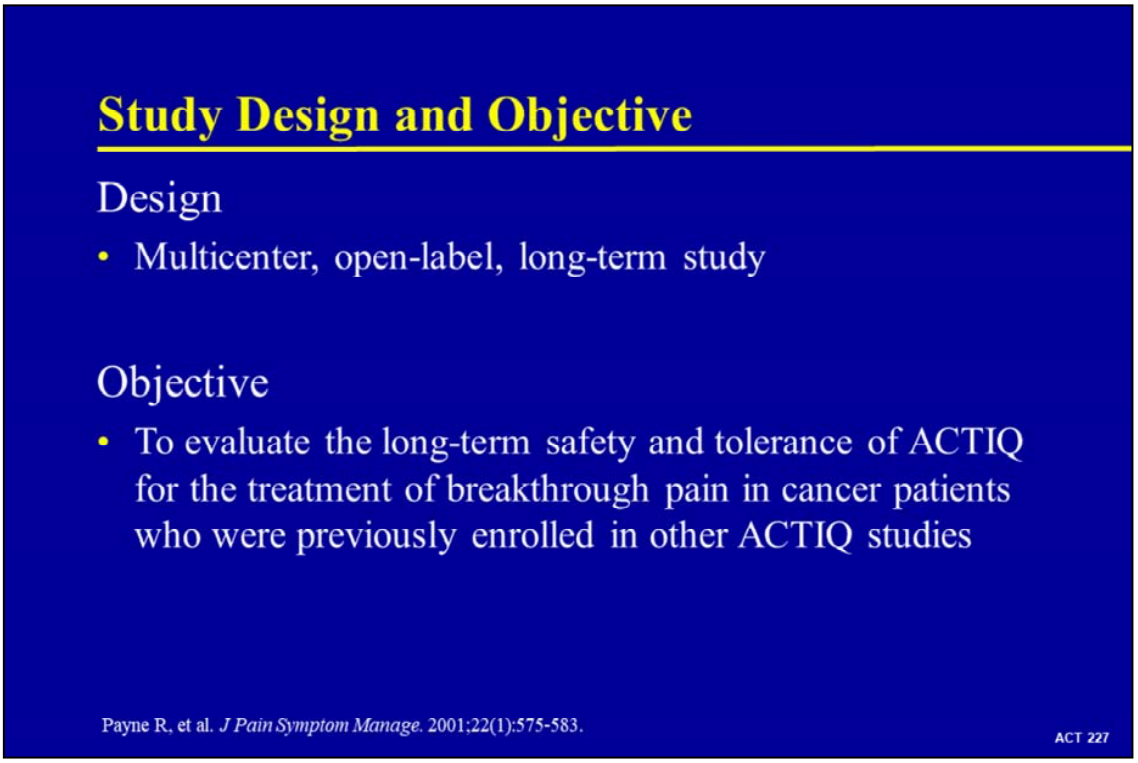
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

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



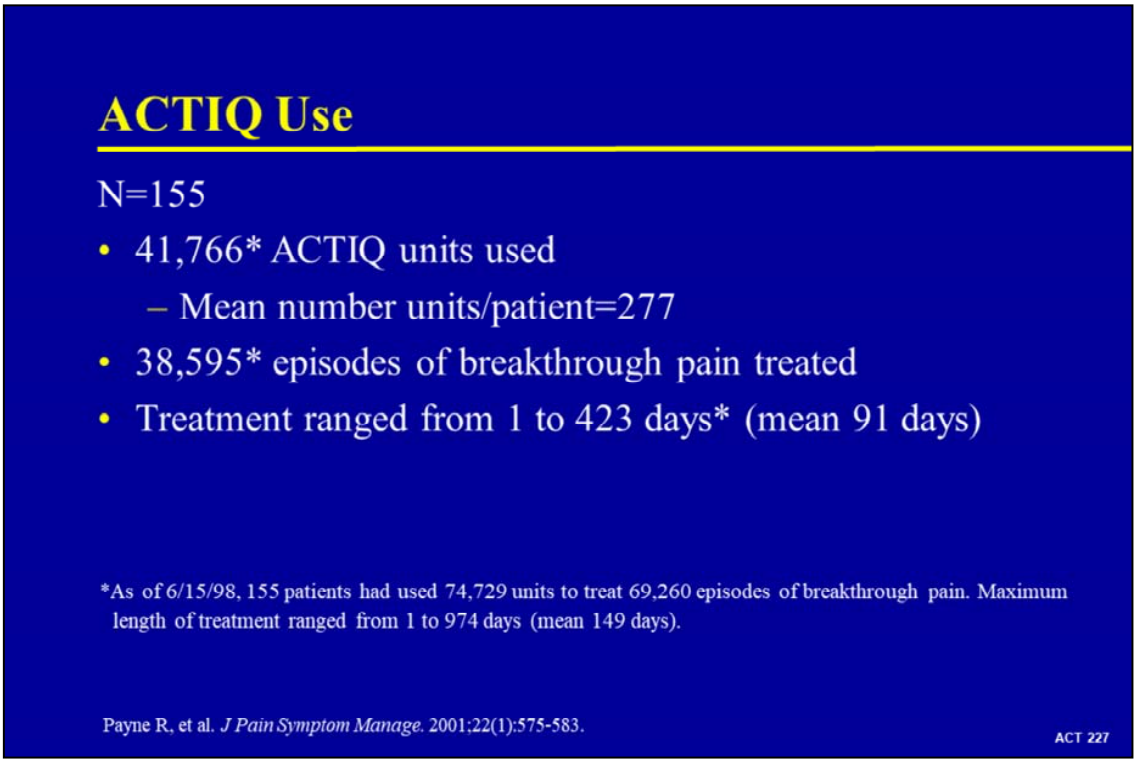
This section includes data from patients who enrolled in the long-term study and who had completed a 4-month block of study participation or had withdrawn since 7/15/96 and before 11/15/96. Some slides in this module contain updated data (from patients who had completed a 4-month block of study participation 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

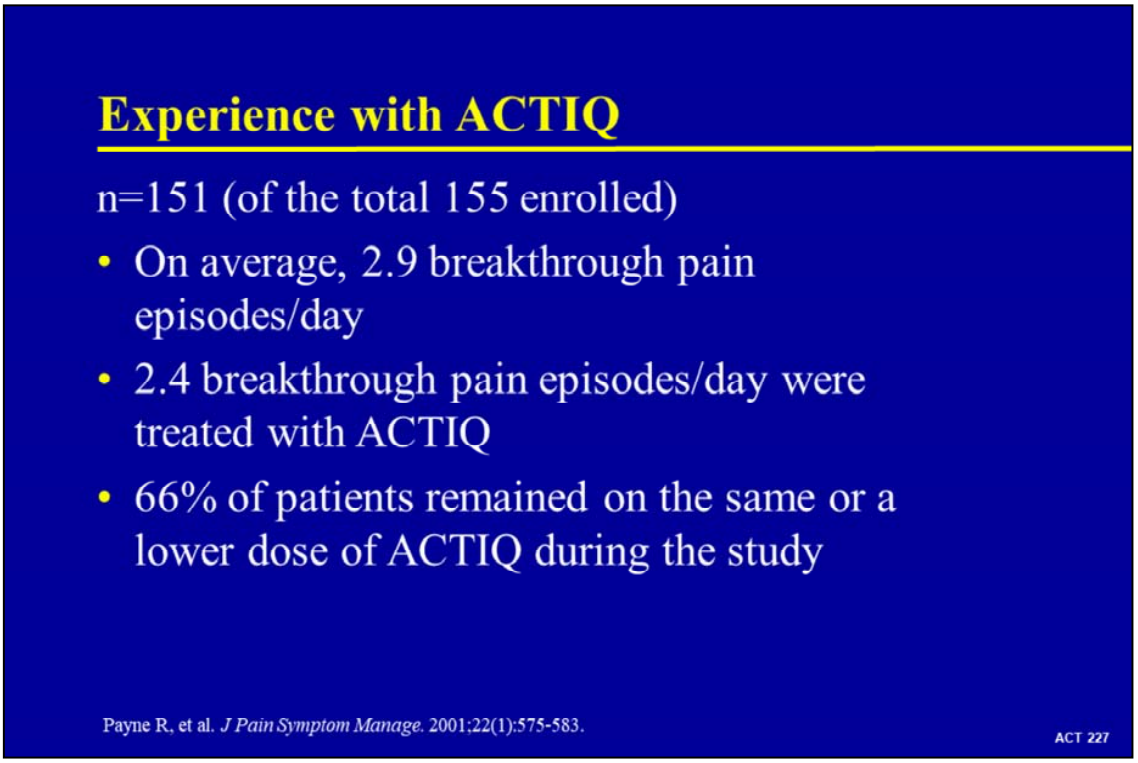
The objective of the study was to evaluate the long-term safety of ACTIQ in patients with BTCP.



ACTIQ Use

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).



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.

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.

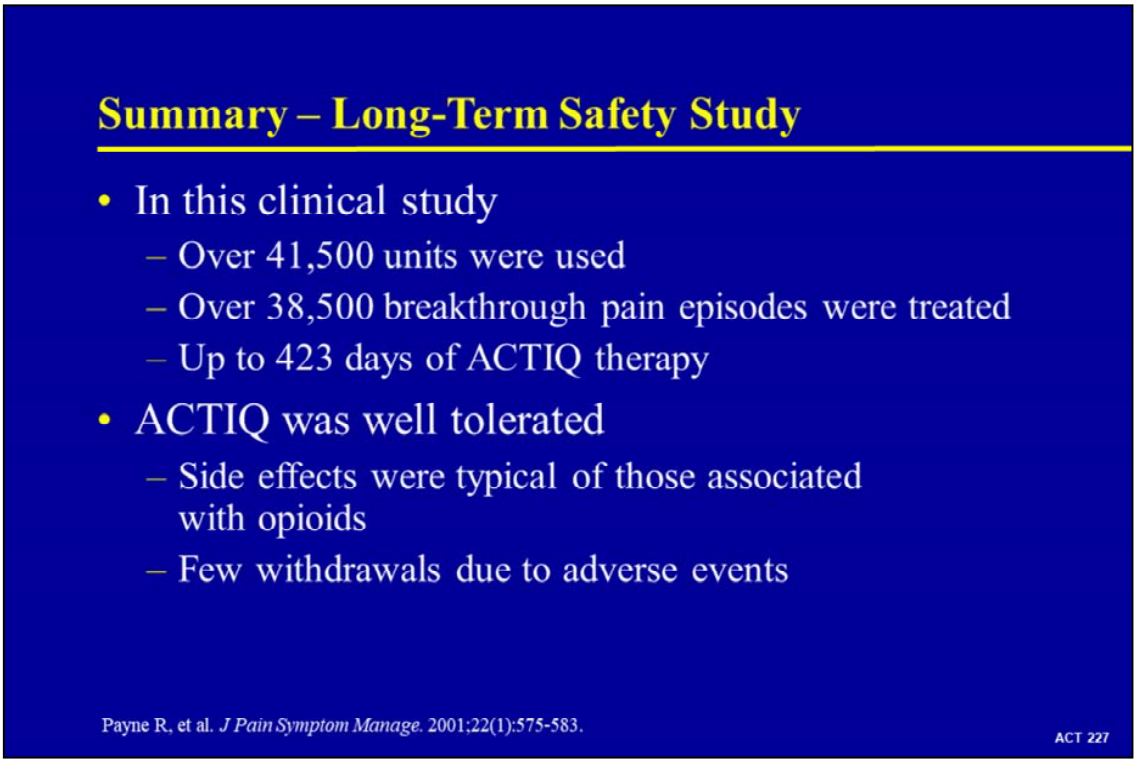
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

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.



Study Results

In this clinical study

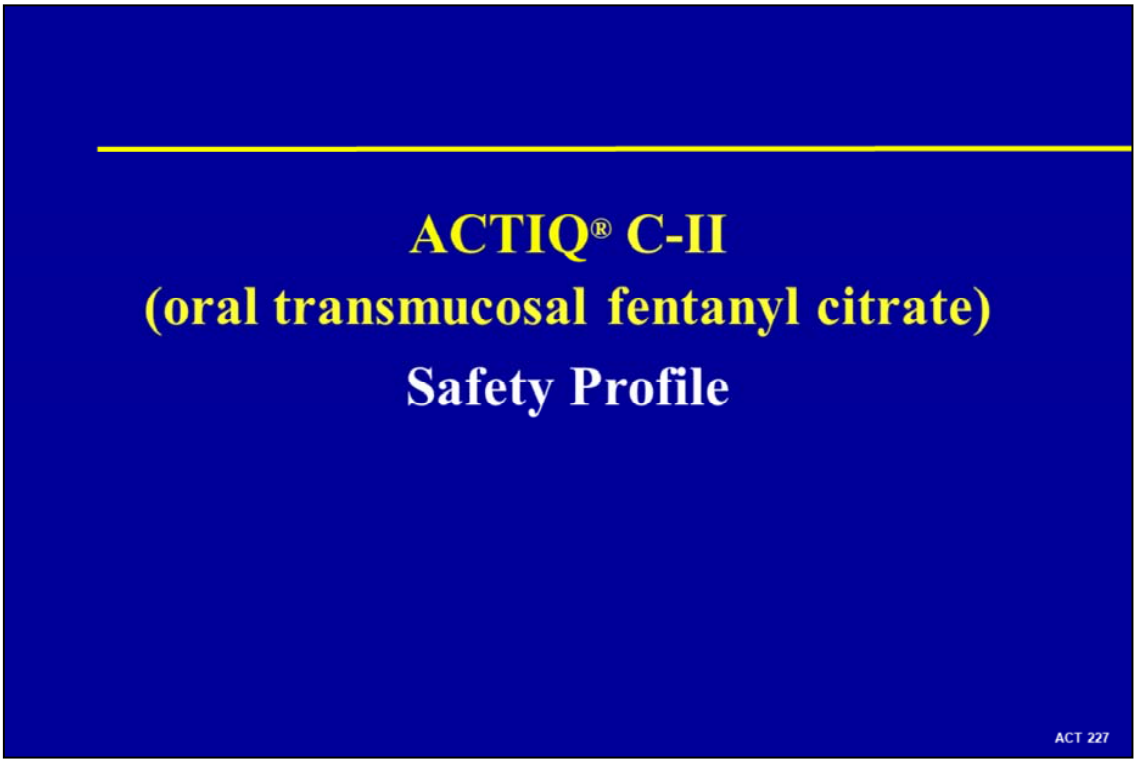
- Over 41,500 ACTIQ units were used
- More than 38,500 episodes of breakthrough pain were treated
- Up to 423 days of ACTIQ therapy
- Very few withdrawals due to adverse events related to ACTIQ

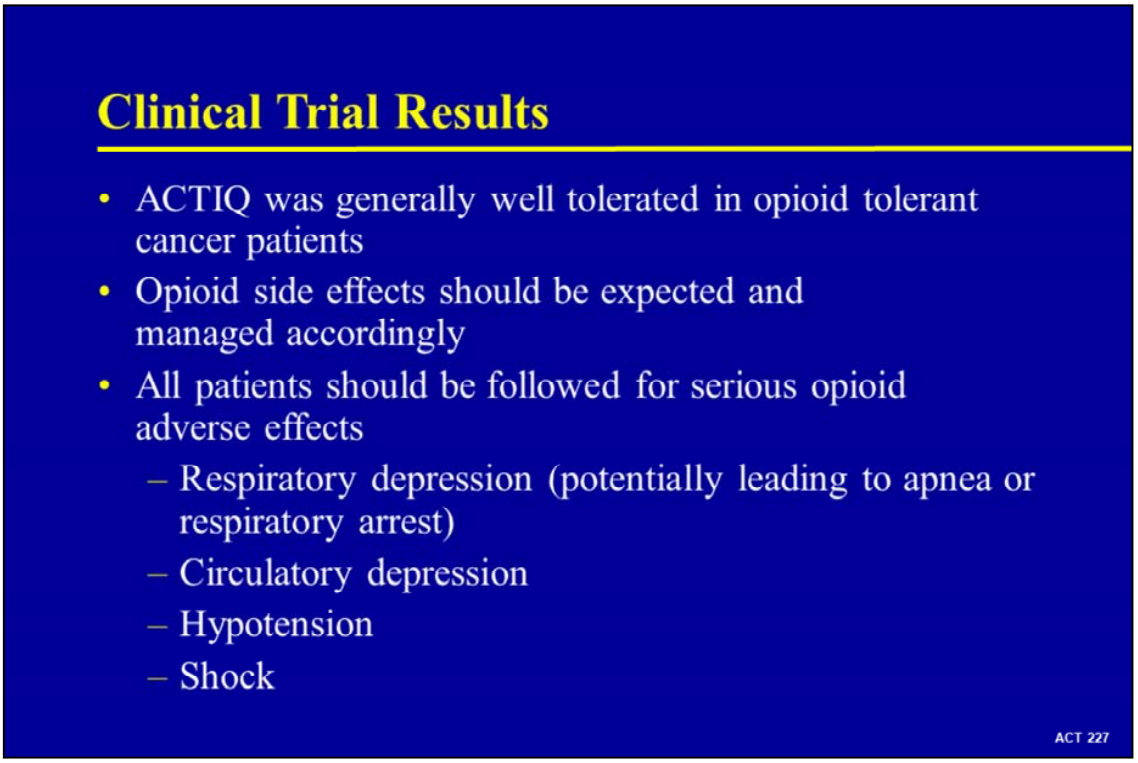
Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.

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

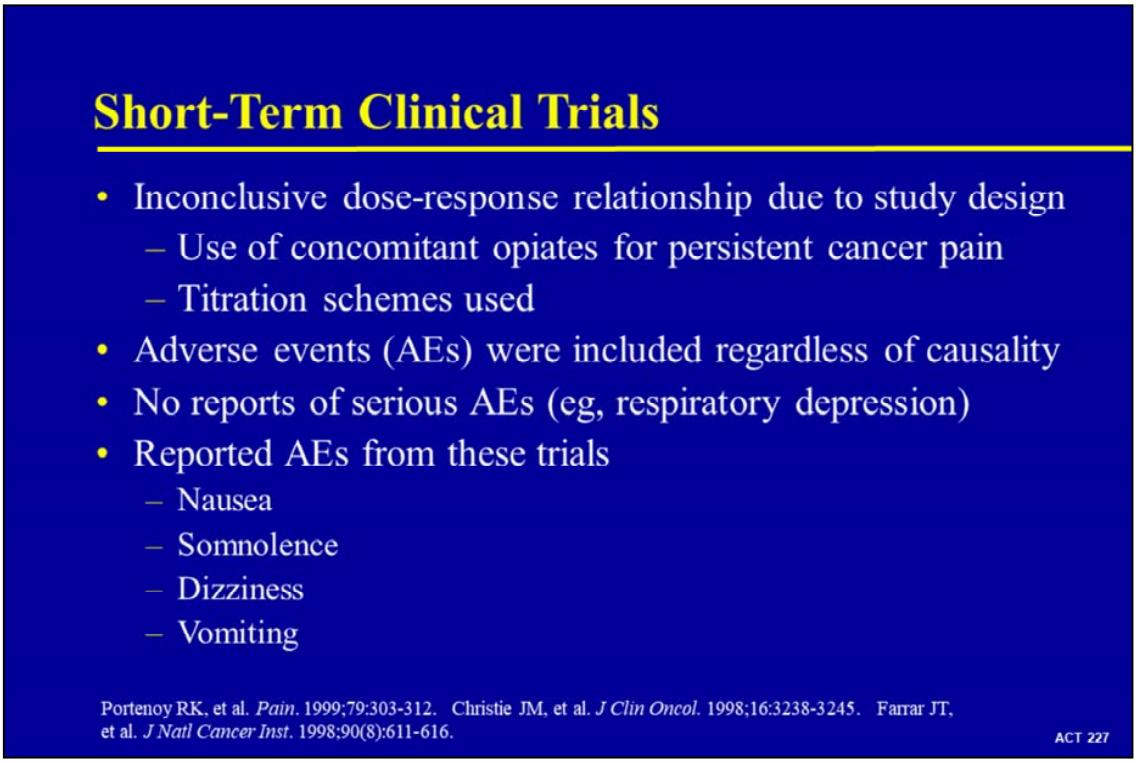


The safety of ACTIQ has been evaluated in 257 opioid-tolerant chronic cancer pain patients. The duration of ACTIQ use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

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.



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.

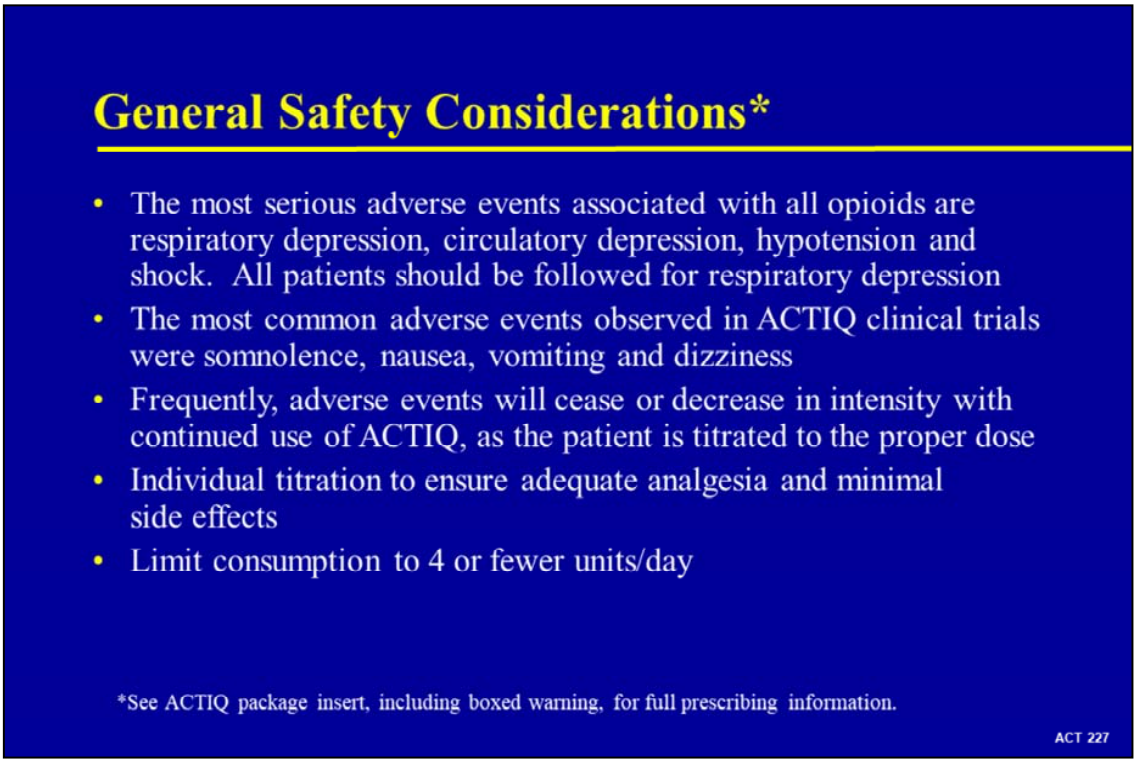
A long-term extension study was conducted in 155 patients with malignancy and BTCP who were treated for an average of 129 days. Data are available for 151 of these patients. Table 4 of the package insert lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during 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.



PRECAUTIONS

General

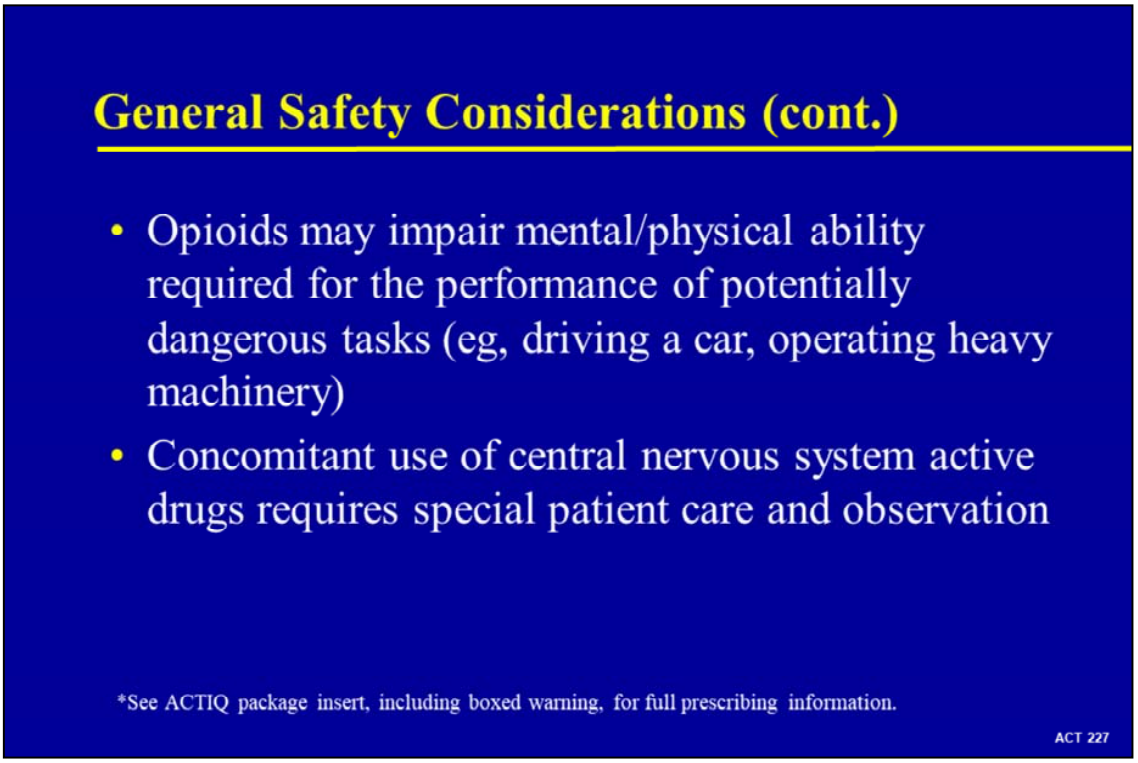
The initial dose of ACTIQ to treat episodes of BTCP should be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

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

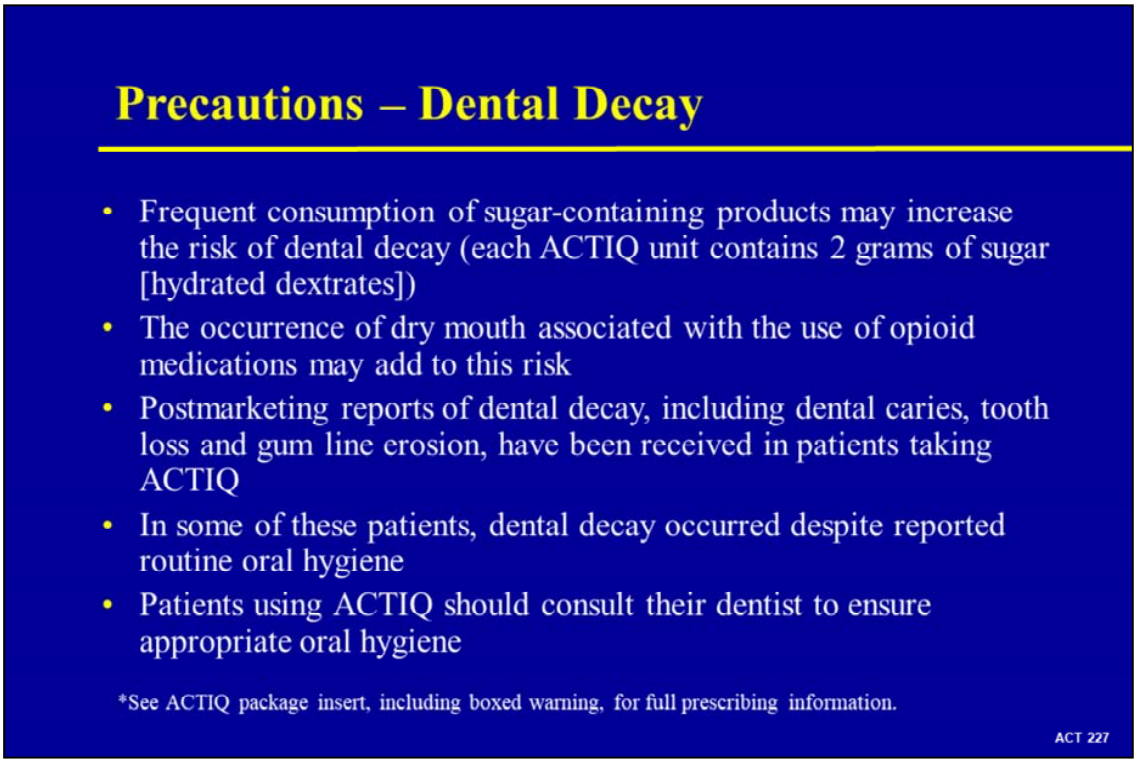
***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 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.)



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.

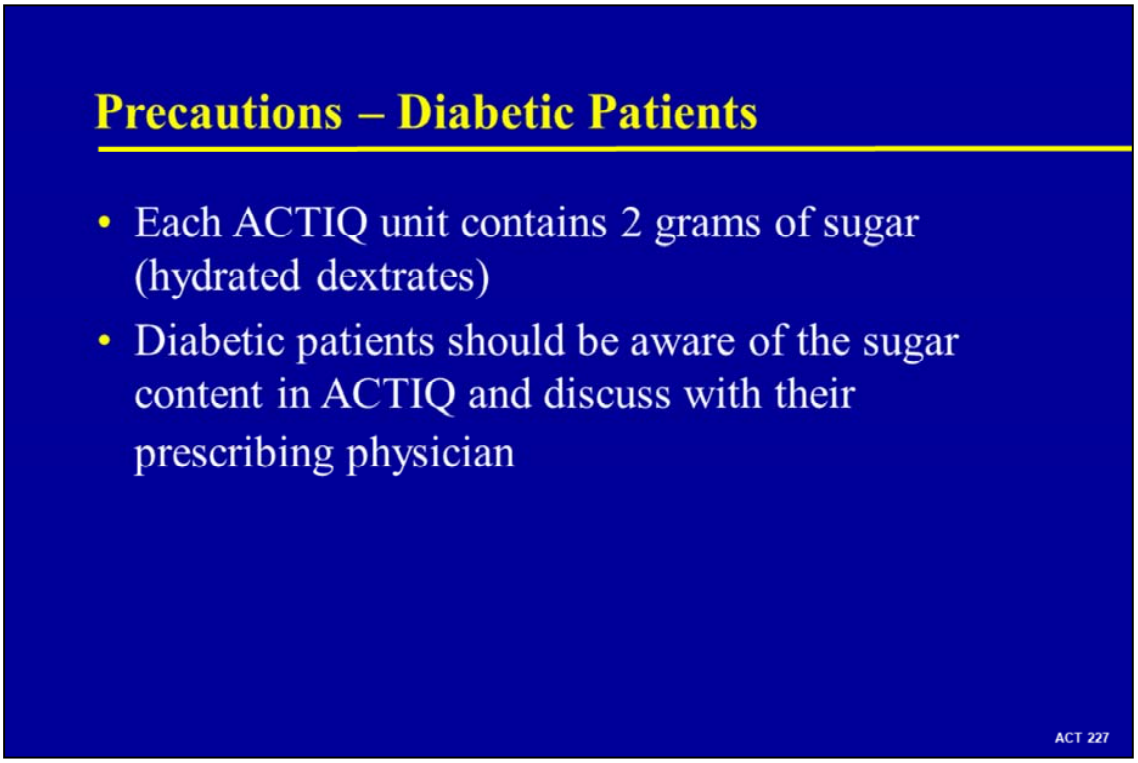


PRECAUTIONS – Information for Patients and Their Caregivers

Dental Decay

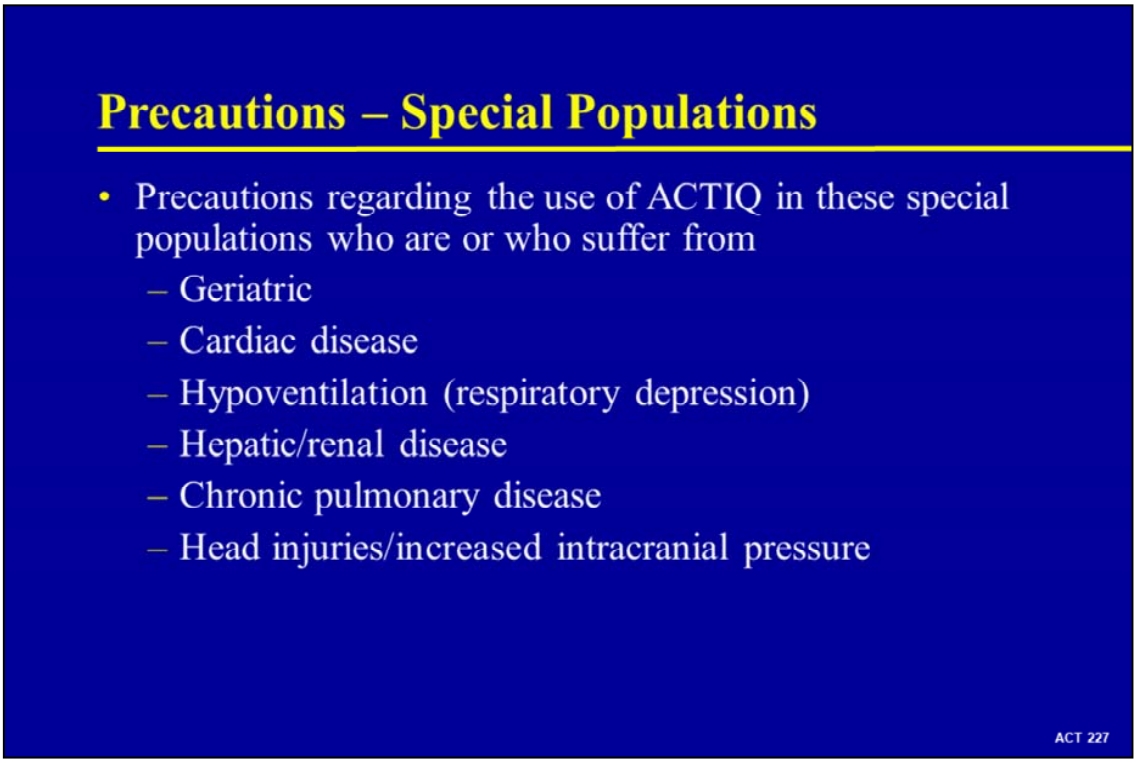
Frequent consumption of sugar-containing products may increase the risk of dental decay (each ACTIQ unit contains 2 grams of sugar [hydrated dextrates]). The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

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 – 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.



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

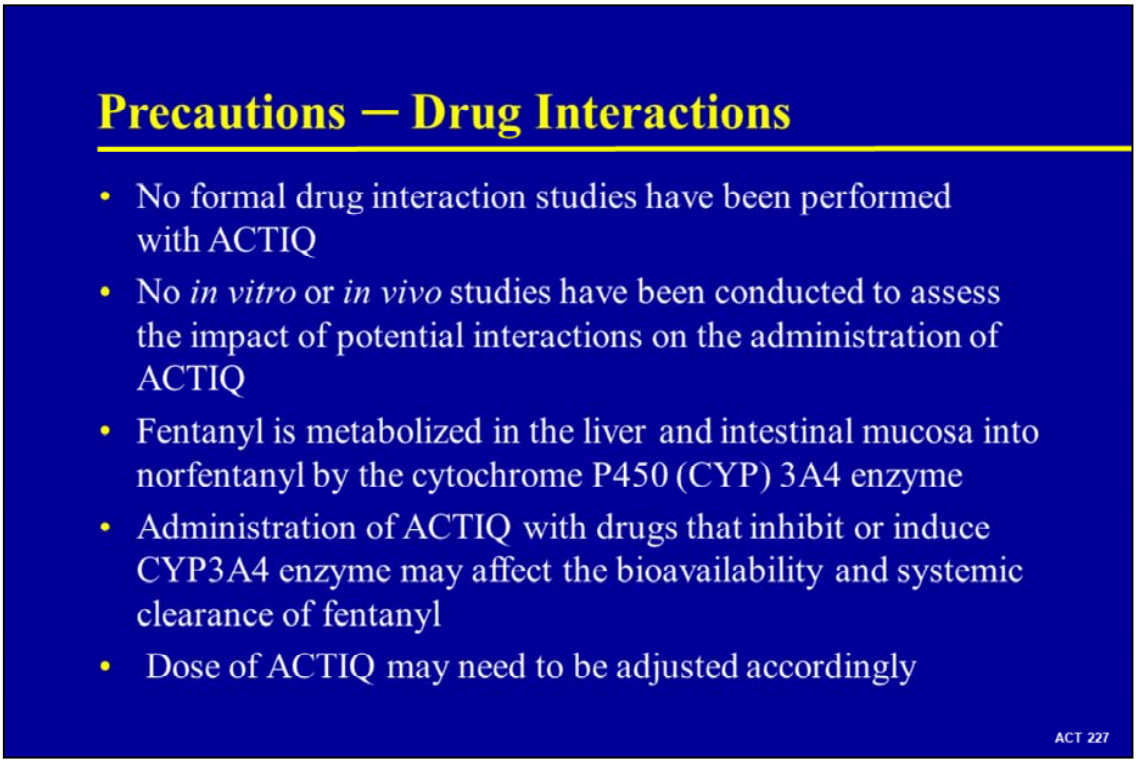
ACTIQ should be administered with caution to patients with liver or kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs and effects on plasma binding proteins (see PHARMACOKINETICS).

Chronic Pulmonary Disease

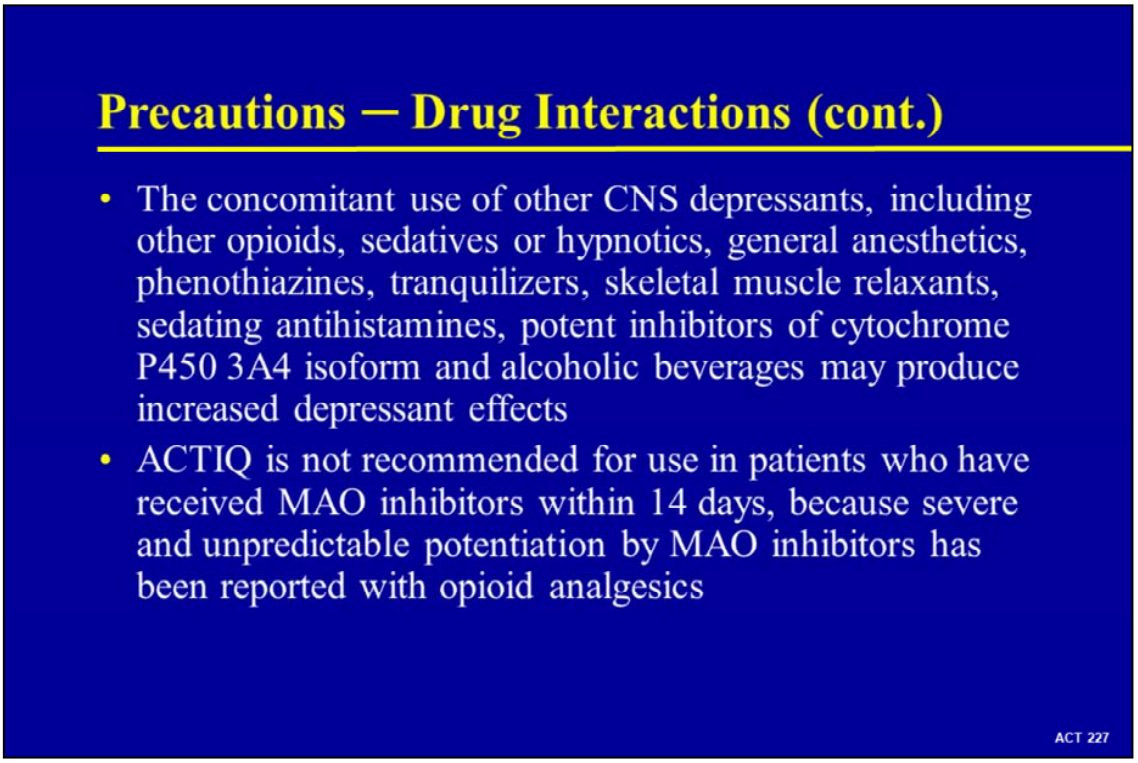
Because potent opioids can cause hypoventilation, ACTIQ should be titrated with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of ACTIQ may further decrease respiratory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

Head Injuries and Increased Intracranial Pressure

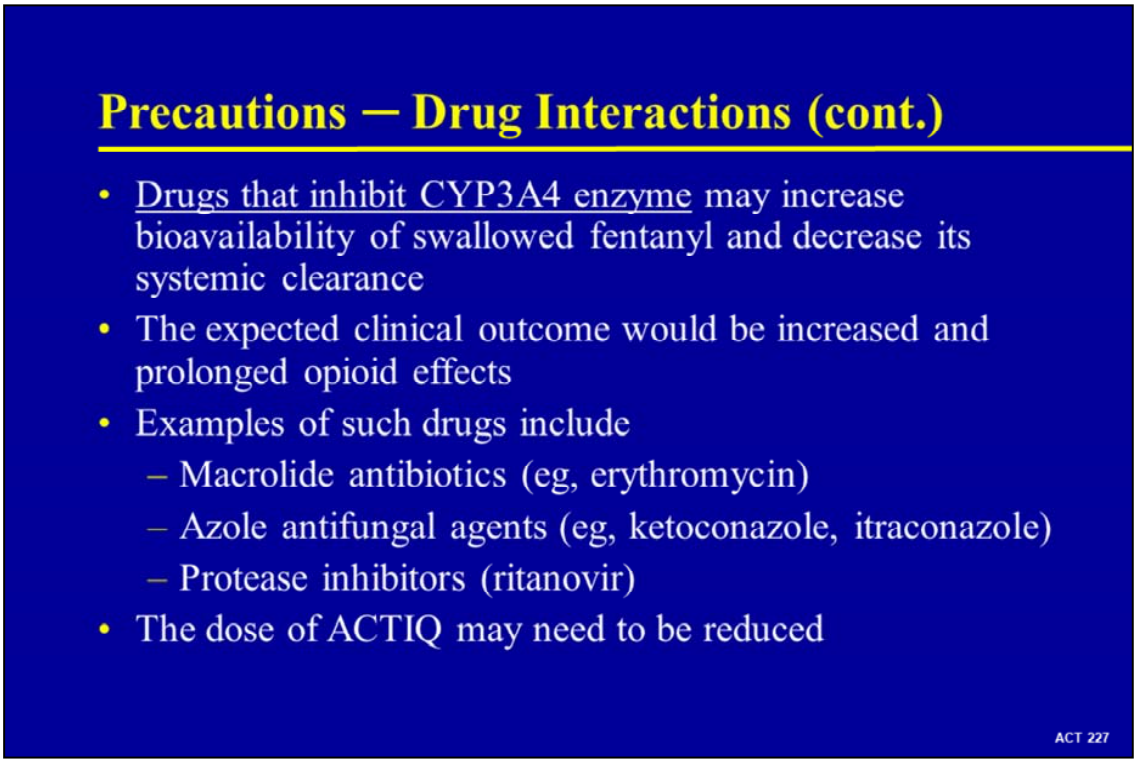
ACTIQ should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head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



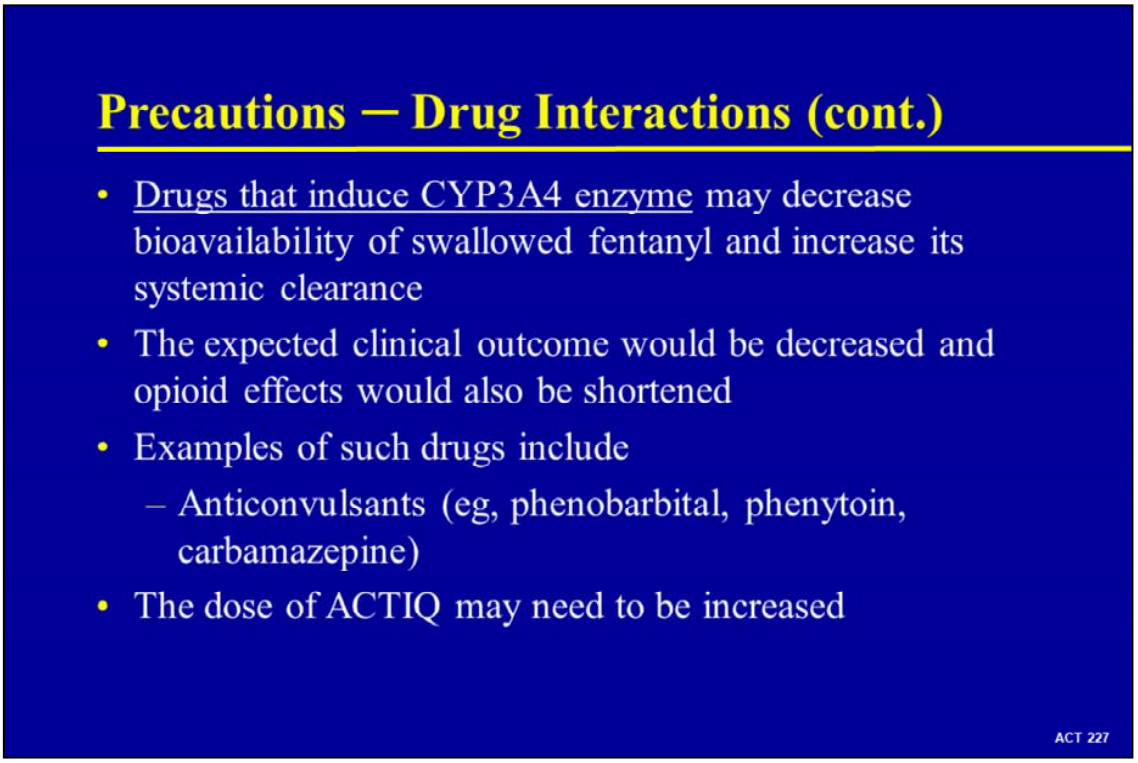
Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by the cytochrome P450 3A4 isoform. Drugs that inhibit P450 3A4 activity may increase the bioavailability of swallowed fentanyl (by decreasing intestinal and hepatic first-pass metabolism) and may decrease the systemic clearance 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.



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.



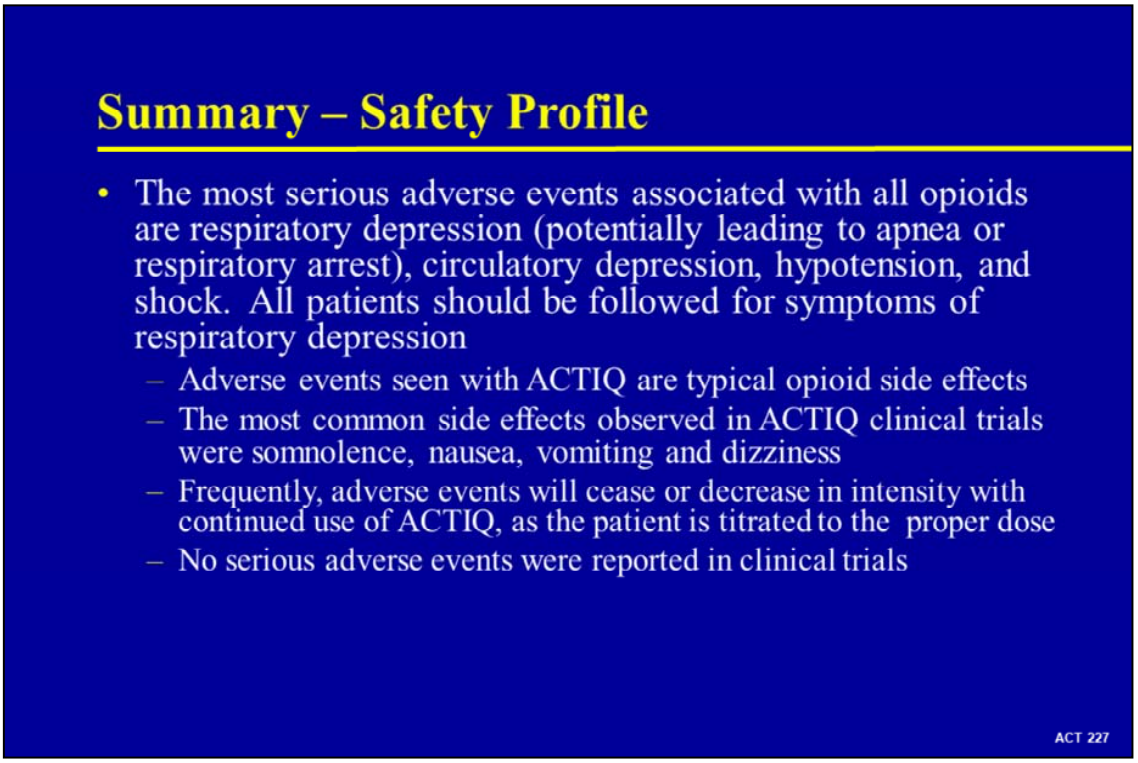
Patients who begin or end therapy with potent inhibitors of P450 3A4 such as macrolide antibiotics (eg, erythromycin), azole antifungal agents (eg, ketoconazole and itraconazole), and protease inhibitors (eg, ritanovir) while receiving ACTIQ should be monitored for a change in opioid effects and, if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



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.

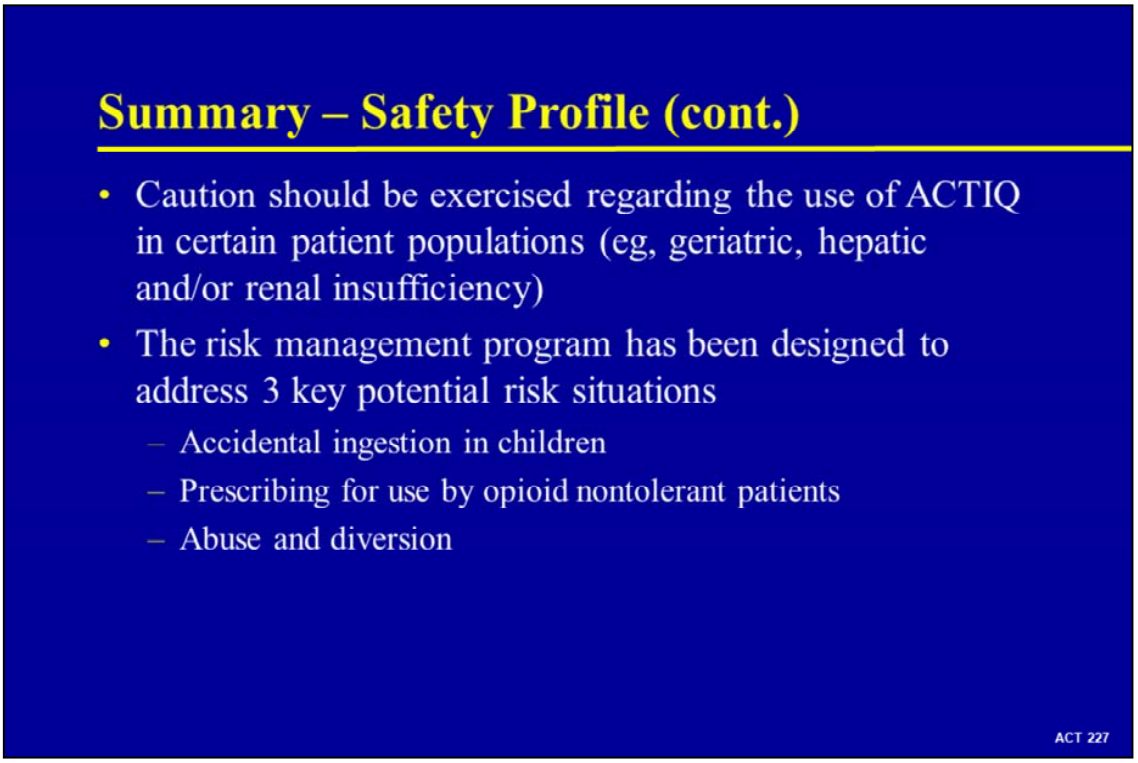
However, no *in vitro* or *in vivo* studies have been performed to assess the impact of these potential interactions on the administration of ACTIQ.

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.



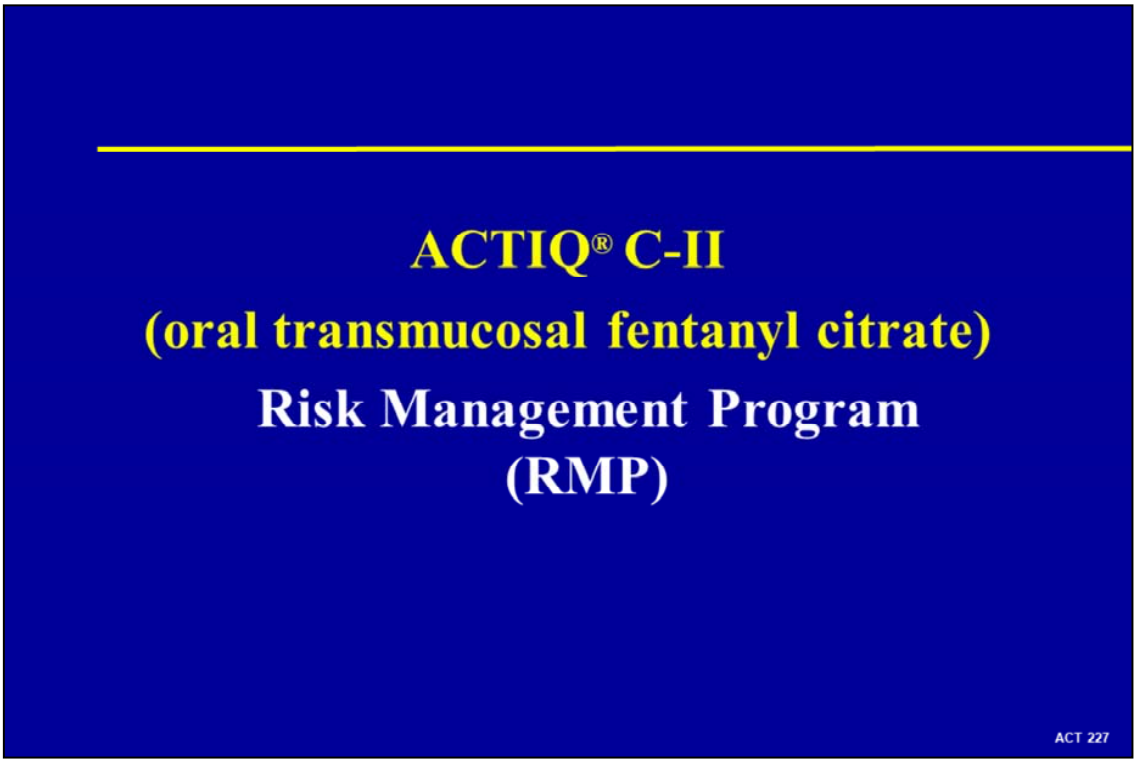
Important Warnings

- 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



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

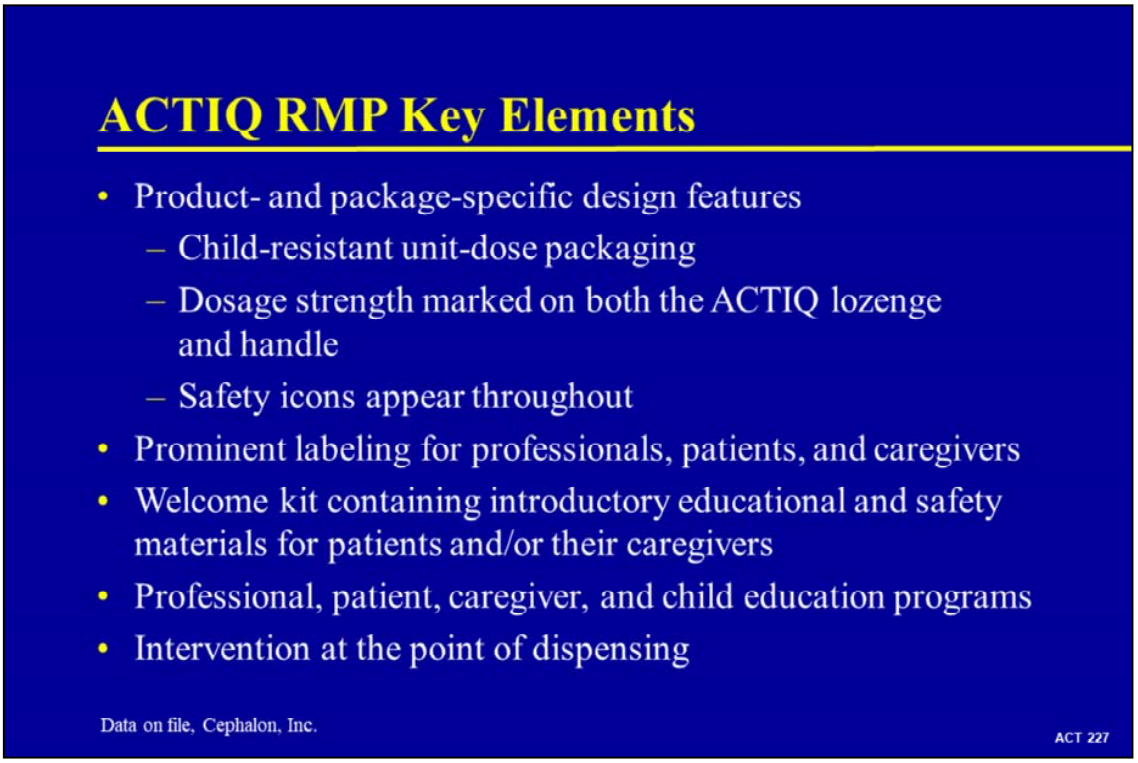

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Risk Management Program
(RMP)
ACT 227

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.

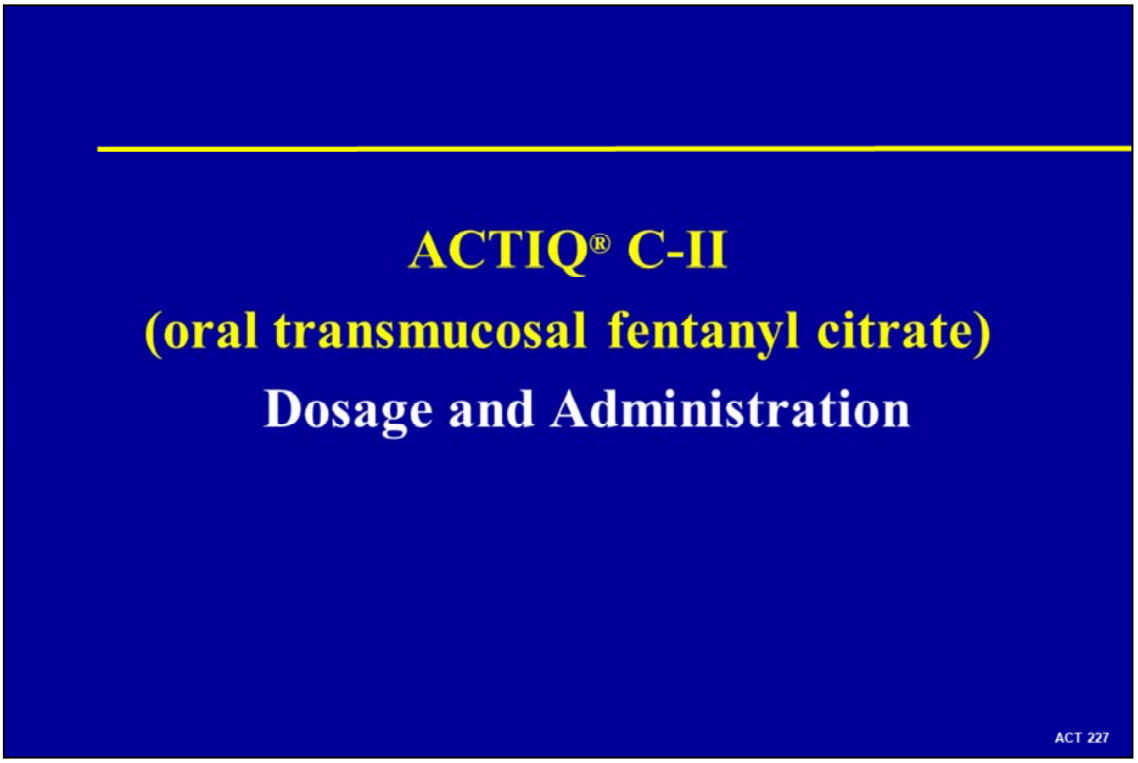
***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer pain.** Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid nontolerant patients.

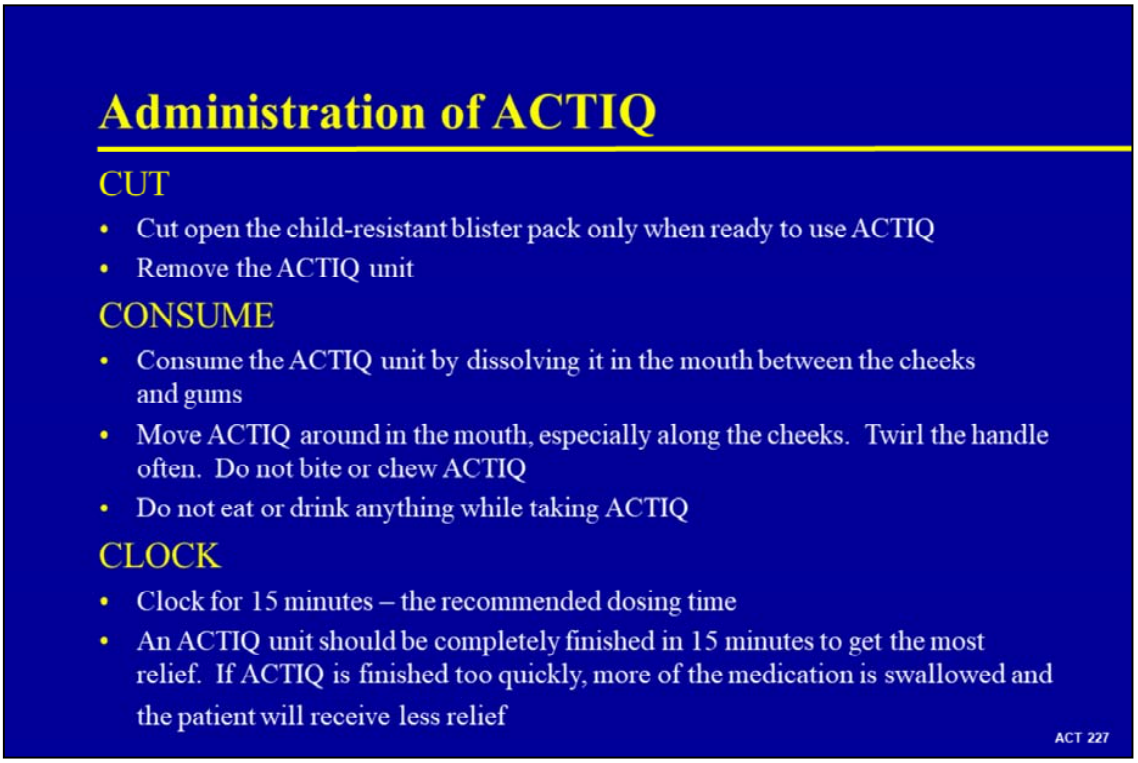
Fentanyl is a Schedule II opioid and thus, has the potential for diversion and abuse, which is the third general area addressed in the ACTIQ Risk Management Program.



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 is 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

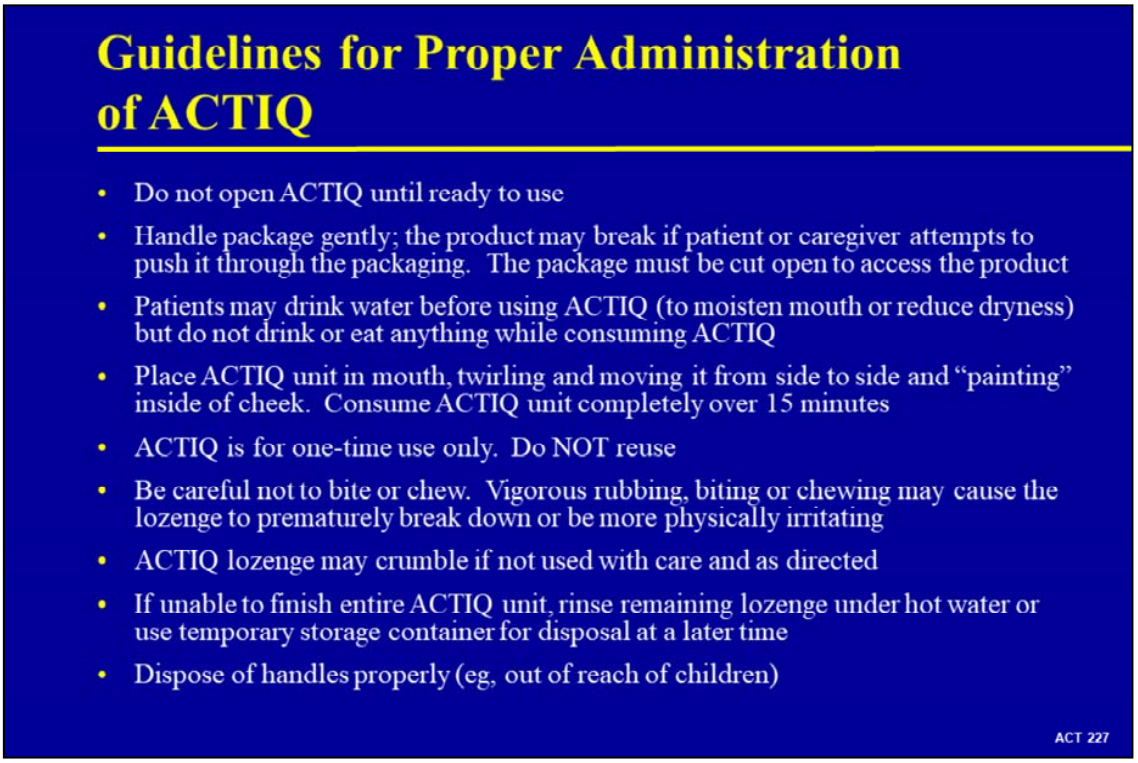


Administration of ACTIQ

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.



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 should 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.

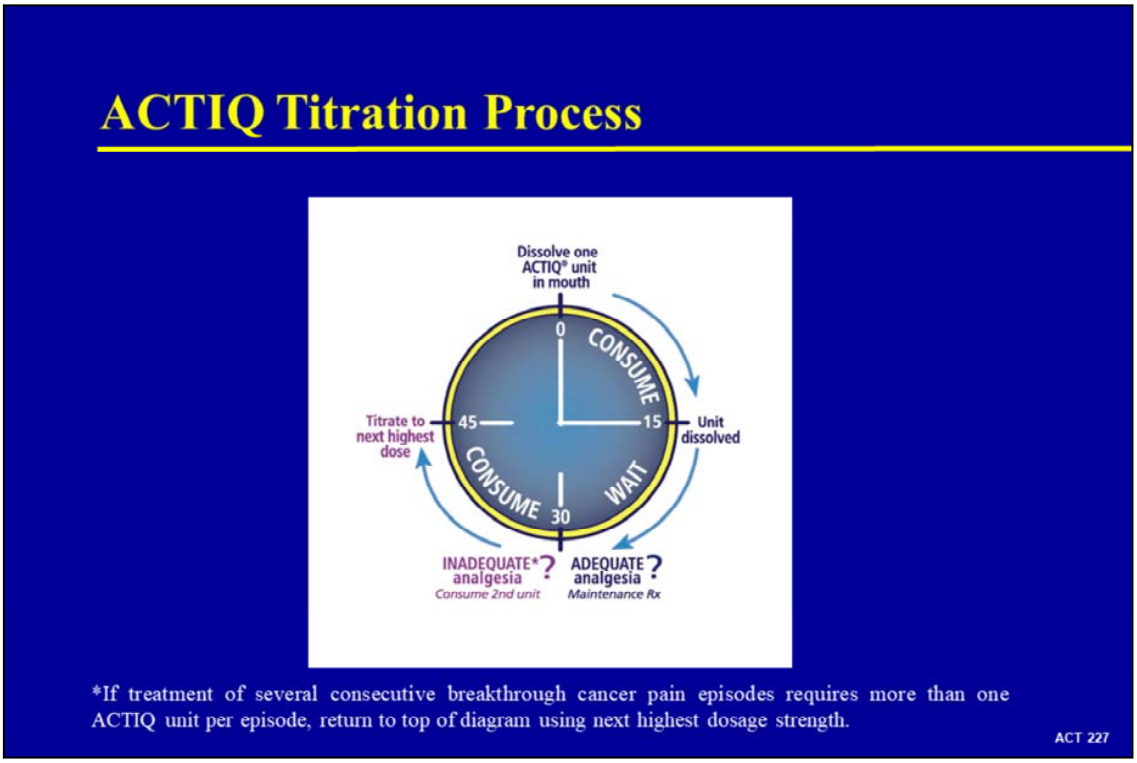
ACTIQ is for one-time use only. Do NOT reuse.

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).



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.

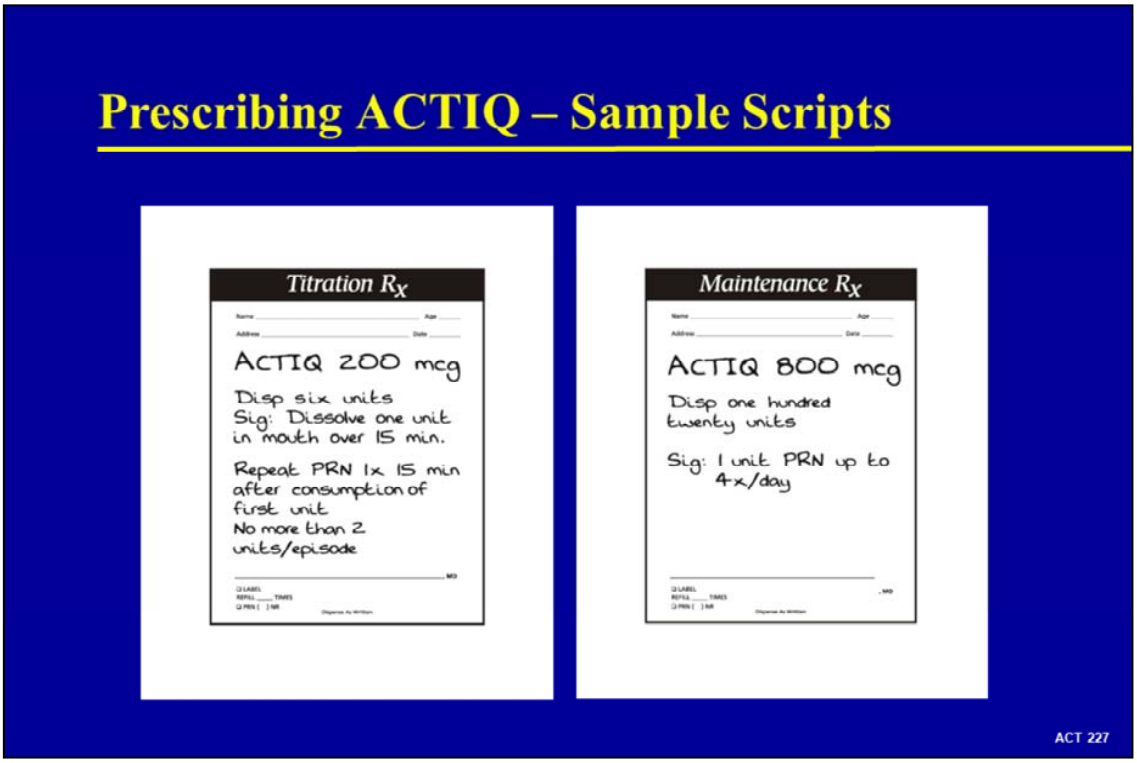
To achieve maximum relief, patients should finish the ACTIQ unit completely in 15 minutes. If they finish too quickly, or bite and swallow the matrix, they will swallow more of the medicine and experience less relief. Longer or shorter consumption times than the recommended 15 minutes may produce less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

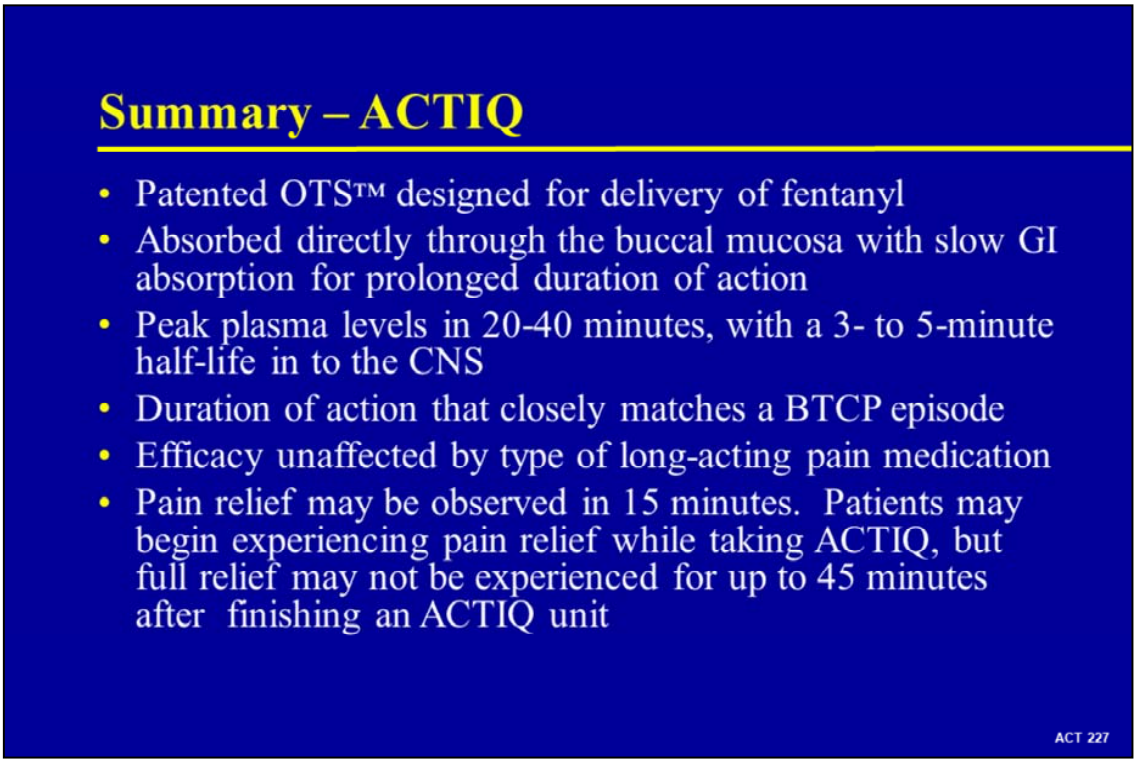
If treatment of several consecutive breakthrough cancer pain episodes requires more than 1 ACTIQ unit per episode, return to the top of the diagram using next highest dosage strength.

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]

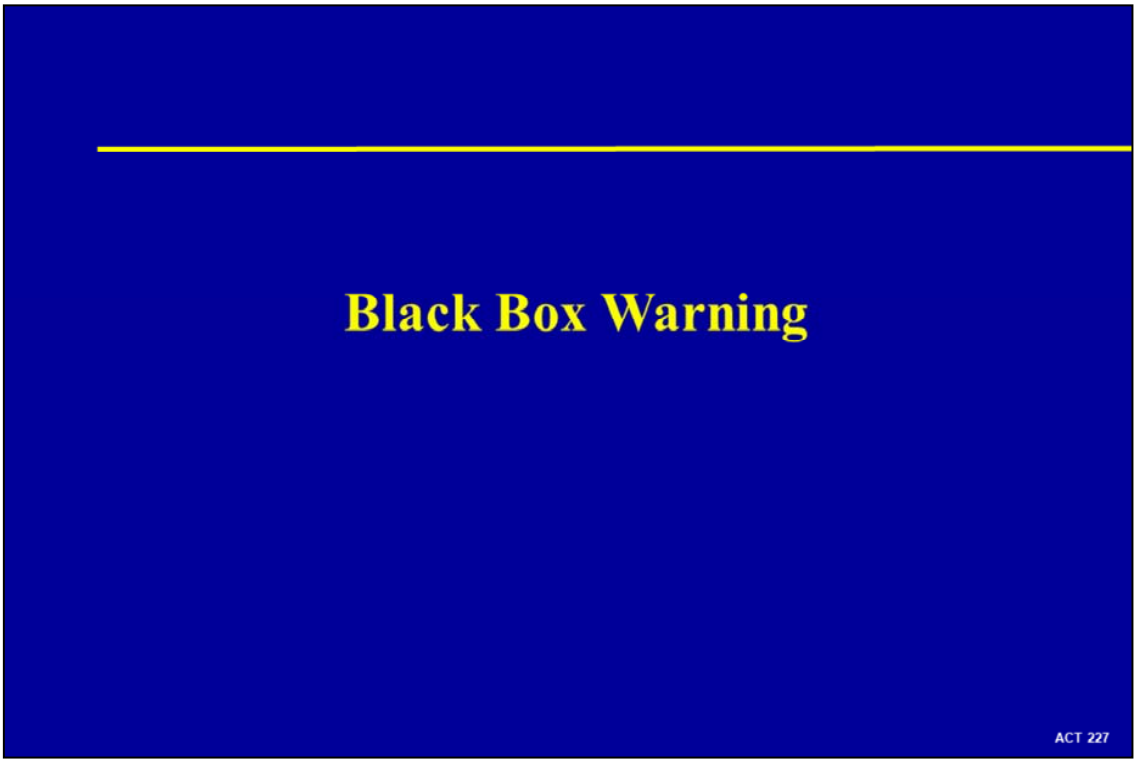


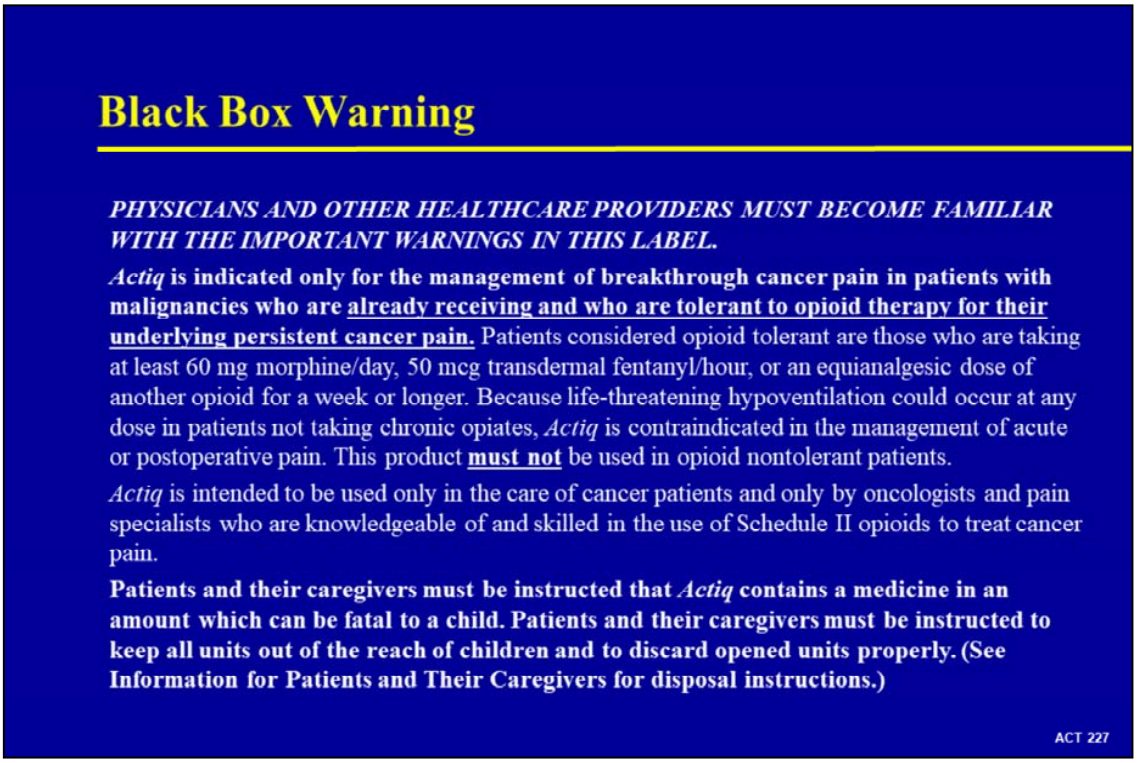
The goal of titration is to provide the patient with adequate analgesia while minimizing side effects. During the titration process, no more than 2 units should be taken for each pain episode, and once a successful maintenance dose has been found, patients should limit their consumption to 4 or fewer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



- Patented OTS™ designed for delivery of fentanyl
- Rapidly absorbed 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 into 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 relief while taking ACTIQ, but full relief may not be experienced for up to 45 minutes after finishing an ACTIQ unit

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
ACT 227



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.)

References

ACT 227

References

- 1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence, and characteristics. *Pain*. 1990;41:273-281.
- 2. Jacox A, Carr DB, Payne R, et al. Cancer Pain Management: Clinical Practice Guideline No. 9. Rockville, MD: US Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; March 1994. AHCPR publication No. 94-0592.
- 3. Mercadante S, Maddaloni S, Roccella S, Salvaggio L. Predictive factors in advanced cancer pain treated only by analgesics. *Pain*. 1992;50:151-155.
- 4. Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. *Pain*. 1991;47:129-134.
- 5. Ashby MA, Fleming BG, Brooksbank M, et al. Description of a mechanistic approach to pain management in advanced cancer: preliminary report. *Pain*. 1992;51:153-161.
- 6. Fine PF, Busch MA. Characterization of breakthrough pain by hospice patients and their caregivers. *J Pain Symptom Manage*. 1998;16:179-183.
- 7. Portenoy RK. et al. Breakthrough Pain: Characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129-134.

ACT 227

References (cont.)

- 8. Caraceni A, Portenoy RK. Breakthrough pain characteristics and syndromes in patients with cancer pain. An international survey. *Palliat Med*. 2004;18:177-183.
- 9. Stanley TH, Hague B, Mock DL, et al. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. *Anesth Analg*. 1989;69:21-27.
- 10. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet*. 1983;8:422-446.
- 11. Streisand JB, Varvel JR, Stanski DR, et al. Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology*. 1991;75:223-229.
- 12. Simmonds MA. Management of breakthrough pain due to cancer. *Oncology (Huntingt)*. 1999;13:1103-1108;discussion 1110,1113-1114.
- 13. Data on file, Cephalon, Inc.

ACT 227

References (cont.)

- 14. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther*. 1988;44:335-337.
- 15. Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metab Dispos*. 1997 Sep;25(9):1072-80.
- 16. DeVane CL. Pharmacogenetics and drug metabolism of newer antidepressant agents. *J Clin Psychiatry*. 1994;55(12, suppl):38-45.
- 17. Wilkinson GR. Clearance approaches in pharmacology. *Pharmacol Rev*. 1987;39: 1-47.
- 18. Bartkowski RR, Goldberg ME, Huffnagle S, et al. Sufentanil disposition - is it affected by erythromycin administration? *Anesthesiology*. 1993;78:260-265.
- 19. Kharasch ED, Mautz D, Bowdle TA. Variability in alfentanil pharmacokinetics: The essential role of cytochrome P4503A. *Anesthesiology*. 1994;8 1:A38 1.

ACT 227

References (cont.)

- 20. Bartkowski RR, Goldberg ME, Larijani GE, et al. Inhibition of alfentanil metabolism by eryhtromycin. *Clin Pharmacol Ther.* 1989;46:99-102.
- 21. Portenoy RK, Payne R, Coluzzi P, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain*. 1999;79:303-312.
- 22. Christie JM, Simmonds M, Patt R, et al. Dose-titration, multicenter study of oral transmucosal fentanyl citrate (ACTIQ) for the treatment of breakthrough pain in cancer patients using transdermal fentanyl. *J Clin Oncol*. 1998;16(10):3238-3245.
- 23. Mercadante S, Armata M, Salvaggio L. Pain characteristics of advanced lung cancer patients referred to a palliative care service. *Pain*. 1994;59:141-145.

ACT 227