From:	Buhrmaster, Alissa (The Selva Group)
To:	Pyfer, Andy; Menna, Adrien
CC:	Priddle Fowler, Julie (The Selva Group)
Sent:	3/29/2006 10:17:16 PM
Subject:	Slide Decks - La Jolla National Speaker Training - June 11, 2005
Attachments:	La Jolla Abuse - Webster.ppt; La Jolla ACTIQ References.pdf; La Jolla Core Slide Kit.pdf; La Jolla Intro - Robinson.ppt; La Jolla Pharmacoeconomic-Manage Care - Shoemaker.ppt; La Jolla Pharmacology-Resp Depr-Safety - Gudin.ppt; La Jolla Promo Slide Kit.pdf; La Jolla Supplemental Slide Sheet.pdf

Slide Decks and Binder Inserts from:

National Speaker Training
Hilton La Jolla Torrey Pines
La Jolla, California
Saturday, June 11, 2005

Abuse & Addiction - Webster
ACTIQ References
Core Slide Kit
Intro - Robinson
Pharmacoeconomics/Manage Care - Shoemaker
Pharmacology/Resp Depr/Safety - Gudin
Promotional Slide Kit
Supplemental Slide Sheet

File Provided Natively

File Provided Natively

File Provided Natively

File Provided Natively

File Provided Natively

Additional ACTIQ® references

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Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain.* 2005;9:195-206.

Burton AW, Driver LC, Mendoza TR, Syed G. Oral transmucosal fentanyl citrate in the outpatient management of severe cancer pain crises: a retrospective case series. *Clin J Pain.* 2004;20:195-197.

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ACTIQ® C-II
(oral transmucosal fentanyl citrate)

ACT 225

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.)

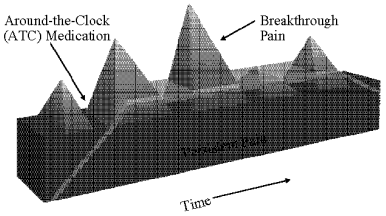
ACT 225

Components of Chronic Cancer Pain

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

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

Components of Moderate-to-Severe Cancer Pain



ACT 225

Characteristics of Breakthrough Cancer Pain

- Moderate-to-severe intensity
- Rapid onset (peaks in <3 minutes in 43% of patients)
- Often unpredictable, strikes without warning
- Relatively short duration
  - On average, lasts for up to 30 minutes
- Frequency: 1-4 episodes per day
- Incident/activity related
  - Movement
  - Coughing/sneezing
  - Touch
- Idiopathic/spontaneous
- End-of-dose failure

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

ACT 225

ACTIQ Indication

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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

ACT 225

Fentanyl Characteristics

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

American Hospital Formulary Service (AHFS), 2003.

ACT 225

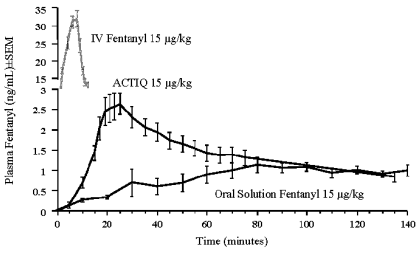
Attributes of ACTIQ

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

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

ACT 225

Fentanyl Concentration-Time Profiles – Different Routes of Administration

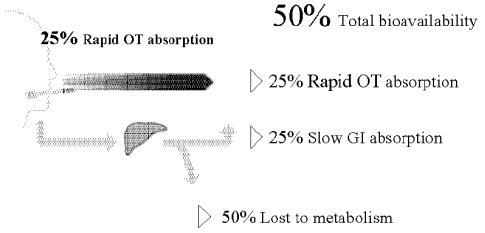


Adapted from Streisand JB, et al. *Anesthesiology*. 1991;75:223-229.

ACT 225

Total Fentanyl Bioavailability Following ACTIQ Administration Is 50%

After standardized consumption time of 15 minutes*



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

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

ACT 225

Pharmacodynamics – Onset of Pain Relief

- Goal: onset of pain relief that is similar to onset of BTCP episode
  - Once in the bloodstream, fentanyl is rapidly distributed to the CNS (a process with a 3- to 5-minute half-life)
  - Pain relief was observed at 15 minutes following administration, the first time point measured. Pain relief was still seen at 60 minutes following administration, the last time point measured
  - Longer or shorter consumption times may produce less efficacy than reported in ACTIQ clinical trials

ACTIQ Package Insert. Rev. August 2004.

ACT 225

Pharmacodynamics – Duration of Pain Relief

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

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

ACT 225

ACTIQ Clinical Trials

- Dose-titration studies
- Placebo-controlled study
- Long-term safety study

ACT 225

Summary – Dose-Titration Studies

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

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

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

ACT 225

Summary – Placebo-Controlled Study

- ACTIQ was more effective than placebo for breakthrough pain in cancer patients receiving oral opioids or transdermal fentanyl
- The successful dose of ACTIQ is determined by titration and cannot be predicted by the baseline opioid dose
- The most common side effects – dizziness, somnolence, and nausea – are typical of opioids and did not limit ACTIQ use
- 93% (74/80 patients) chose to continue taking ACTIQ for their breakthrough pain

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

ACT 225

Summary – Long-Term Safety Study

- In this clinical study
  - 41,766 units were used
  - 38,595 breakthrough pain episodes were treated
  - Up to 423 days of ACTIQ therapy
  - 2.4 breakthrough pain episodes/day were treated with ACTIQ
  - 66% of patients remained on the same or a lower dose of ACTIQ during the study
- ACTIQ was well tolerated
  - The most common side effects observed were somnolence, nausea, vomiting, and dizziness
  - Few withdrawals due to adverse events

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

ACT 225

General Risk Information*

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

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 225

General Risk Information (cont.)*

- Opioids may impair mental/physical ability required for the performance of potentially dangerous tasks (eg, driving a car, operating heavy machinery)
- Concomitant use of central nervous system active drugs requires special patient care and observation
- Administration of ACTIQ with drugs that inhibit or induce CYP3A4 enzyme may affect the bioavailability and systemic clearance of fentanyl
  - Dose of ACTIQ may need to be adjusted accordingly
- Caution should be exercised regarding the use of ACTIQ in certain patient populations (eg, geriatric, hepatic, and/or renal insufficiency)

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 225

General Risk Information (cont.)*

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 may add to this risk
- Postmarketing reports of dental decay, including dental caries, tooth loss, and gum line erosion, have been received in patients taking ACTIQ
- In some of these patients, dental decay occurred despite reported routine oral hygiene
- Patients using ACTIQ should consult their dentist to ensure appropriate oral hygiene

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 225

ACTIQ RMP Key Elements

- The RMP has been designed to address 3 key potential risk situations
  - Accidental ingestion in children
  - Improper patient selection
  - Abuse and diversion
- Product- and package-specific design features
- Prominent labeling for professionals, patients, and caregivers
- Welcome kit containing introductory educational and safety materials for patients and/or their caregivers
- Professional, patient, caregiver, and child education programs
- Intervention at the point of dispensing

Data on file, Cephalon, Inc.

ACT 225

Administration of ACTIQ

CUT

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

CONSUME

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

CLOCK

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

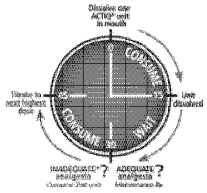
ACT 225

Guidelines for Proper Administration of ACTIQ

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

ACT 225

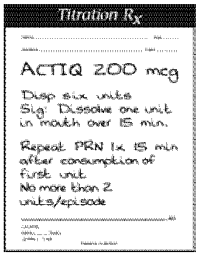
ACTIQ Titration Process

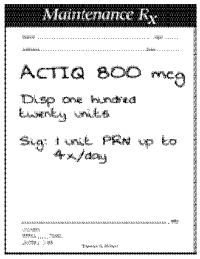


*If treatment of several consecutive breakthrough cancer pain episodes requires more than one ACTIQ unit per episode, return to top of diagram using next highest dosage strength.

ACT 225

Prescribing ACTIQ – Sample Scripts





ACT 225

Summary – ACTIQ

- Patented OTS™ designed for delivery of fentanyl
- Absorbed directly through the buccal mucosa with slow GI absorption for prolonged duration of action
- Peak plasma levels in 20-40 minutes, with a 3- to 5-minute half-life in to the CNS
- Duration of action that closely matches a BTCP episode
- Efficacy unaffected by type of long-acting pain medication
- Pain relief was observed at 15 minutes following administration, the first time point measured. Pain relief was still seen at 60 minutes following administration, the last time point measured
- The most serious adverse events associated with all opioids are respiratory depression, circulatory depression, hypotension, and shock. All patients should be followed for respiratory depression

See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 225

References

- 1. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence, and characteristics. *Pain*. 1990;41:273-281.
- 2. Mercadante S, Maddaloni S, Roccella S, Salvaggio L. Predictive factors in advanced cancer pain treated only by analgesics. *Pain*. 1992;50:151-155.
- 3. Banning A, Sjogren P, Henriksen H. Treatment outcome in a multidisciplinary cancer pain clinic. *Pain*. 1991;47:129-134.
- 4. 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.
- 5. Fine PF, Busch MA. Characterization of breakthrough pain by hospice patients and their caregivers. *J Pain Symptom Manage*. 1998;16:179-183.
- 6. Portenoy RK. Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129-134.

ACT 225

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

ACT 225

File Provided Natively

File Provided Natively

File Provided Natively

File Provided Natively

File Provided Natively

File Provided Natively

Pathophysiology	Dose Ranging Portenoy et al (n=65)[a]	Dose Ranging Christie et al (n=62)[a]	Placebo Farrarr et al (n=92)[b]	Total (n=219)
Nociceptive – Somatic	28 (43%)	34 (55%)	48 (52%)	110 (50%)
Nociceptive - Visceral	15 (23%)	18 (29%)	29 (32%)	62 (28%)
Neuropathic	22 (34%)	10 (16%0	13 (14%)	45 (21%)
Unknown			2 (2%)	2 (1%)

[a] All patients who participated
[b] All patients who participated in the double-blind phase

File Provided Natively

File Provided Natively

ACTIQ® C-II
(oral transmucosal fentanyl citrate)

ACT 227

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ACT 227

Overview of Chronic Cancer Pain

ACT 227

Components of Chronic Cancer Pain

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

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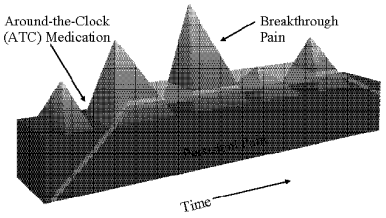
ACT 227

Components of Moderate-to-Severe Cancer Pain



ACT 227

Cancer Pain Assessment

ACT 227

Keys to Appropriate Pain Assessment

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

ACT 227

Pain Assessment Tools: Temporal Nature of Pain

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

ACT 227

Characteristics of Breakthrough Cancer Pain

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

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

ACT 227

Types of Breakthrough Pain

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

ACT 227

Pharmacologic Management of Chronic Cancer Pain

ACT 227

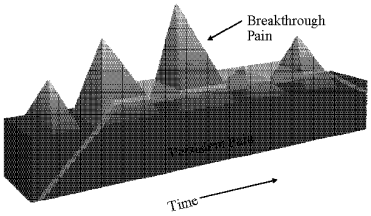
Treatment of Chronic Cancer Pain – Goals of Effective Pharmacologic Management

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

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

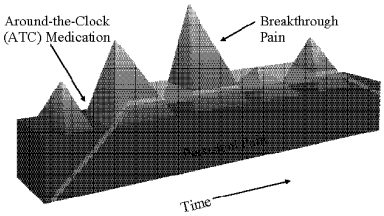
ACT 227

Components of Moderate-to-Severe Cancer Pain



ACT 227

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



ACT 227

Goals of Breakthrough Cancer Pain Medication

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

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

ACT 227

ACTIQ® C-II
(oral transmucosal fentanyl citrate)
Indication

ACT 227

ACTIQ Indication

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.

ACT 227

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

ACT 227

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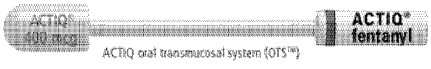
ACT 227

Route of Administration

ACT 227

Oral Transmucosal System (OTS™) Drug Delivery Technology

ACTIQ uses OTS technology to deliver fentanyl



ACT 227

Fentanyl Characteristics

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

American Hospital Formulary Service (AHFS), 2003.

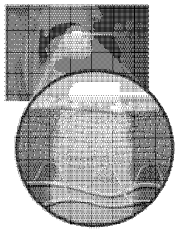
ACT 227

Fentanyl: Routes of Administration

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

ACT 227

Oral Transmucosal Route of Administration

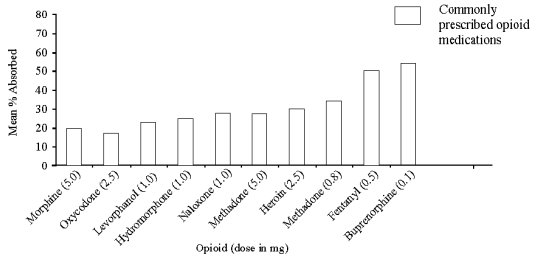


Characteristics of oral mucosa provide an ideal route of administration

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

ACT 227

Absorption of Opioids From Oral Mucosa



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

ACT 227

Lipid Solubility and CNS Equilibrium Times

	Morphine	Oxycodone	Fentanyl
Octanol/H_2O partition coefficient (lipid solubility)	1.4	0.7[1]	813[2]
Keo $T_{1/2}$ (time into CNS)	17 min[3]	N/A	3-5 min[2]

N/A=Not available.

1 - OxyContin PI.
2 - ACTIQ PI.
3 - Kramer TH, d'Amours RH, Buetner C. *Clin Pharmacol Ther.* 1996;59:132.

ACT 227

Optimal Conditions for Absorption Through Oral Mucosa

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

ACT 227

Attributes of ACTIQ

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

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

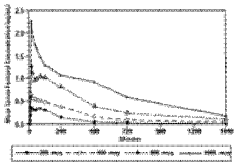
ACT 227

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

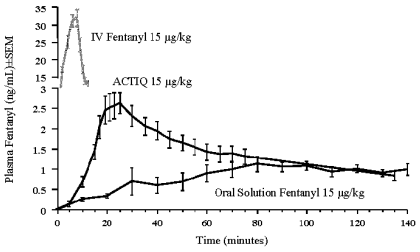
Comparison of Different Formulations of Fentanyl – Parenteral, Oral Solution, Oral Transmucosal

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

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

ACT 227

Fentanyl Concentration-Time Profiles – Different Routes of Administration



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

ACT 227

Fentanyl Pharmacokinetic Parameters – Different Routes of Administration

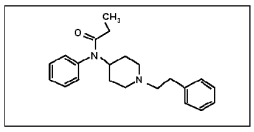
	IV	Oral Solution	ACTIQ
C_{max} (ng/mL)	33.6±5.5	16±0.6	2.8±1.0
T_{max} (min)	N/A	101.3±48.8	23.0±3.4
Bioavailability (F)	1.0	0.32±0.10	0.50±0.11
Percent (%)	100	32	50

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

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

ACT 227

Fentanyl Metabolism

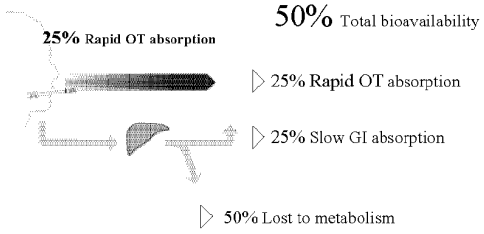


- Metabolized by liver and intestinal microsomes
- Catalyzed predominantly by P450 3A4
- Primary metabolite norfentanyl
  - Not pharmacologically active
  - Renal excretion

ACT 227

Total Fentanyl Bioavailability Following ACTIQ Administration is 50%

After standardized consumption time of 15 minutes*



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

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

ACT 227

Pharmacodynamics – Onset of Pain Relief

- Goal: onset of pain relief that is similar to onset of BTCP episode
  - Once in the bloodstream, fentanyl is rapidly distributed to the CNS (a process with a 3- to 5-minute half-life)
  - Pain relief was observed at 15 minutes following administration, the first time point measured. Pain relief was still seen at 60 minutes following administration, the last time point measured
  - Longer or shorter consumption times may produce less efficacy than reported in ACTIQ clinical trials

ACTIQ Package Insert. Rev. August 2004.

ACT 227

Pharmacodynamics – Duration of Pain Relief

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

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

ACT 227

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

ACT 227

Study Design and Objectives

Study design: multicenter, randomized, double-blind

Primary objective

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

Secondary objectives

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

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

ACT 227

Eligible Patients

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

ACT 227

Study Design

Baseline Phase	ACTIQ Phase
Assess baseline performance of usual supplemental opioid for breakthrough pain	• ACTIQ titration to define successful dose (200 mcg-1600 mcg)* • Assess performance of ACTIQ at successful dose

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

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

ACT 227

Assessment of Breakthrough Pain Treatment

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

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

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

ACT 227

ACTIQ Titration Procedure

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

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

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

ACT 227

Pain Pathophysiology

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

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

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

ACT 227

Patient Completion Status

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

* 4/8 ACTIQ related.
† 3/6 ACTIQ related.
‡ Noncompliance (n=2), vacation, unable to consume first unit, inadequate pain relief.
§ Breakthrough pain ceased, scheduled for chemotherapy, incomplete pain relief, change in ATC dose.

ACT 227

Adverse Events

The most common adverse events (AEs):

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

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

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

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

ACT 227

Summary – Dose-Titration Studies

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

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

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

ACT 227

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

ACT 227

Study Design and Objectives

Study design

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

Primary objective

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

Secondary objectives

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

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

ACT 227

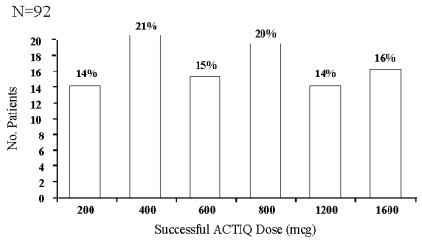
Patient Completion Status

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

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

ACT 227

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



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

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

ACT 227

Medication Performance

- Global satisfaction score (scale 0-4) was significantly higher with ACTIQ than usual supplemental medications
  - 1.98 vs 1.19 (P=0.0001)
- 93% of eligible patients chose to continue using ACTIQ
  - 74/80 patients chose ACTIQ long-term study
  - 6 patients returned to usual supplemental medication

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

ACT 227

Adverse Events

The Most Common AEs in All 130 Patients*		
Dizziness	22	(17%)
Nausea	17	(13%)
Somnolence	11	(8%)
Constipation	7	(5%)
Asthenia	6	(5%)
Confusion	5	(4%)

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

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

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

ACT 227

Summary – Placebo-Controlled Study

- ACTIQ was more effective than placebo for breakthrough pain in cancer patients receiving oral opioids or transdermal fentanyl
- The successful dose of ACTIQ is determined by titration and cannot be predicted by the baseline opioid dose
- The most common side effects – dizziness, somnolence, and nausea – are typical of opioids and did not limit ACTIQ use
- 93% (74/80 patients) chose to continue taking ACTIQ for breakthrough pain

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

ACT 227

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

ACT 227

Study Design and Objective

Design

- Multicenter, open-label, long-term study

Objective

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

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

ACT 227

ACTIQ Use

N=155

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

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

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

ACT 227

Experience with ACTIQ

n=151 (of the total 155 enrolled)

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

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

ACT 227

Adverse Events

Most Common Adverse Events*		
Somnolence	14	(9%)
Constipation	13	(8%)
Nausea	12	(8%)
Dizziness	12	(8%)
Vomiting	8	(5%)

*At least possibly related to ACTIQ.

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

ACT 227

Summary – Long-Term Safety Study

- In this clinical study
  - 41,766 units were used
  - 38,595 breakthrough pain episodes were treated
  - Up to 423 days of ACTIQ therapy
  - 2.4 breakthrough pain episodes/day were treated with ACTIQ
  - 66% of patients remained on the same or a lower dose of ACTIQ during the study
- ACTIQ was well tolerated
  - The most common side effects observed were somnolence, nausea, vomiting, and dizziness
  - Few withdrawals due to adverse events

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

ACT 227

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

ACT 227

Clinical Trial Results

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

ACT 227

Short-Term Clinical Trials

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

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

ACT 227

Long-Term Clinical Trial

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

*Data available for 151 patients.

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

ACT 227

General Risk Information*

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

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 227

General Risk Information (cont.)*

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

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 227

Precautions – Dental Decay*

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

*See ACTIQ Package Insert, including boxed warning, for full prescribing information.

ACT 227

Precautions – Diabetic Patients

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

ACT 227

Precautions – Special Populations

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

ACT 227

Precautions — Drug Interactions

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

ACT 227

Precautions — Drug Interactions (cont.)

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

ACT 227

Precautions — Drug Interactions (cont.)

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

ACT 227

Precautions — Drug Interactions (cont.)

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

ACT 227

Potential for Abuse and Diversion

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

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

ACT 227

Summary – Safety Profile

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

ACT 227

Summary – Safety Profile (cont.)

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

ACT 227

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

ACT 227

ACTIQ Risk Management Program (RMP)

- Benefits of ACTIQ come with potential risks
- The RMP objective is to ensure safe use of the product
- The RMP has been designed to address 3 key potential risk situations
  - Accidental ingestion in children
  - Improper patient selection
  - Abuse and diversion

Data on file, Cephalon, Inc.

ACT 227

ACTIQ RMP Key Elements

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

Data on file, Cephalon, Inc.

ACT 227

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

ACT 227

Administration of ACTIQ

CUT

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

CONSUME

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

CLOCK

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

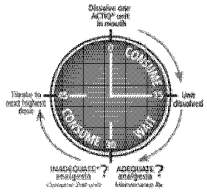
ACT 227

Guidelines for Proper Administration of ACTIQ

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

ACT 227

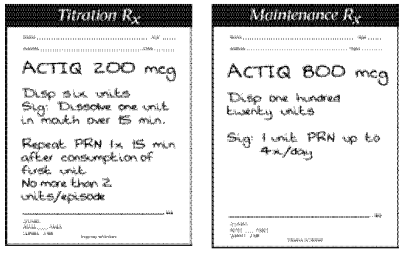
ACTIQ Titration Process



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

ACT 227

Prescribing ACTIQ – Sample Scripts



ACT 227

Summary – ACTIQ

- Patented OTS™ designed for delivery of fentanyl
- Absorbed directly through the buccal mucosa with slow GI absorption for prolonged duration of action
- Peak plasma levels in 20-40 minutes, with a 3- to 5-minute half-life in to the CNS
- Duration of action that closely matches a BTCP episode
- Efficacy unaffected by type of long-acting pain medication
- Pain relief was observed at 15 minutes following administration, the first time point measured. Pain relief was still seen at 60 minutes following administration, the last time point measured
- The most serious adverse events associated with all opioids are respiratory depression, circulatory depression, hypotension, and shock. All patients should be followed for respiratory depression

ACT 227

Black Box Warning

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

References

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References

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Some of the information presented in the supplemental slides is not consistent with the approved product labeling of ACTIQ and is intended only for scientific exchange. These slides can be used when speaking on behalf of Cephalon at MEP programs in response to unsolicited questions from audience members. When appropriate, speakers should also acknowledge that such information is on an unapproved use of ACTIQ and will clarify the drug's indication.