From: Morrison, Jacqueline [/O=CEPHALON/OU=US01 ADMINISTRATIVE GROUP/CN=RECIPIENTS/CN=JMORRISO]
Sent: 1/20/2006 12:17:03 PM
To: Sales PCS Northwest [salespcsnorthwest@cephalon.com]
Subject: Actiq slide kit
Attachments: actiqbriefslides.ppt

Hi Everyone,

Attached is the brief Actiq slide deck, make a bunch of copies and keep them in your car incase you need them for MEP's. When you make your copies print at least three slides on each page, this will cut down on the number of pages you have to copy. This is the brief slide deck it has about 25 slides.

Let me know if you have any questions.

Regards,

Jackie Morrison
Area Manager- Pacific Northwest
Pain Care Division
Cephalon
415-613-1493

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.)

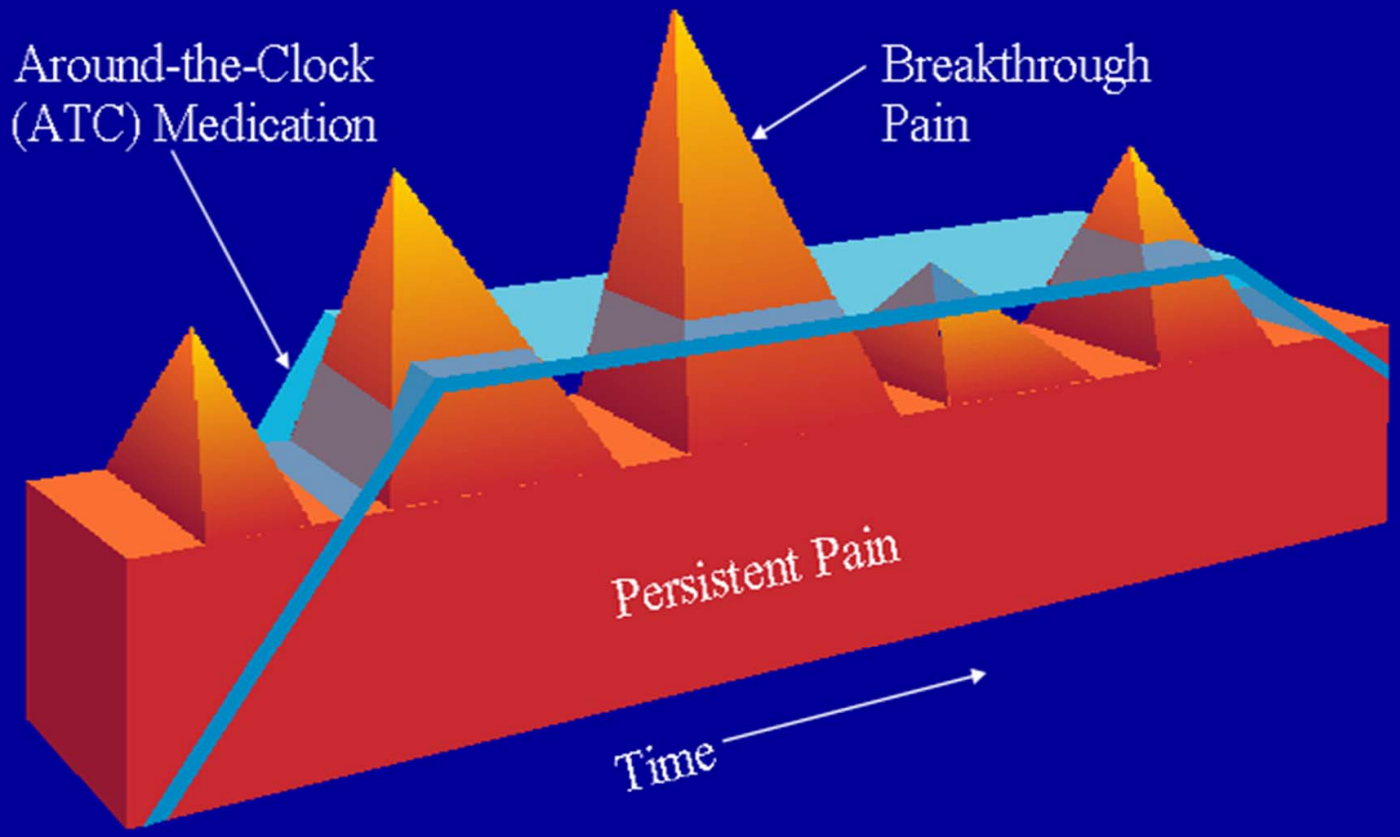
ACT 225

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 Chronic 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

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

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 ($T_{½}$) ~7 hours
  - Pharmacologically inactive metabolites (eg, norfentanyl) are primarily excreted in the urine

American Hospital Formulary Service (AHFS), 2003.

ACT 225

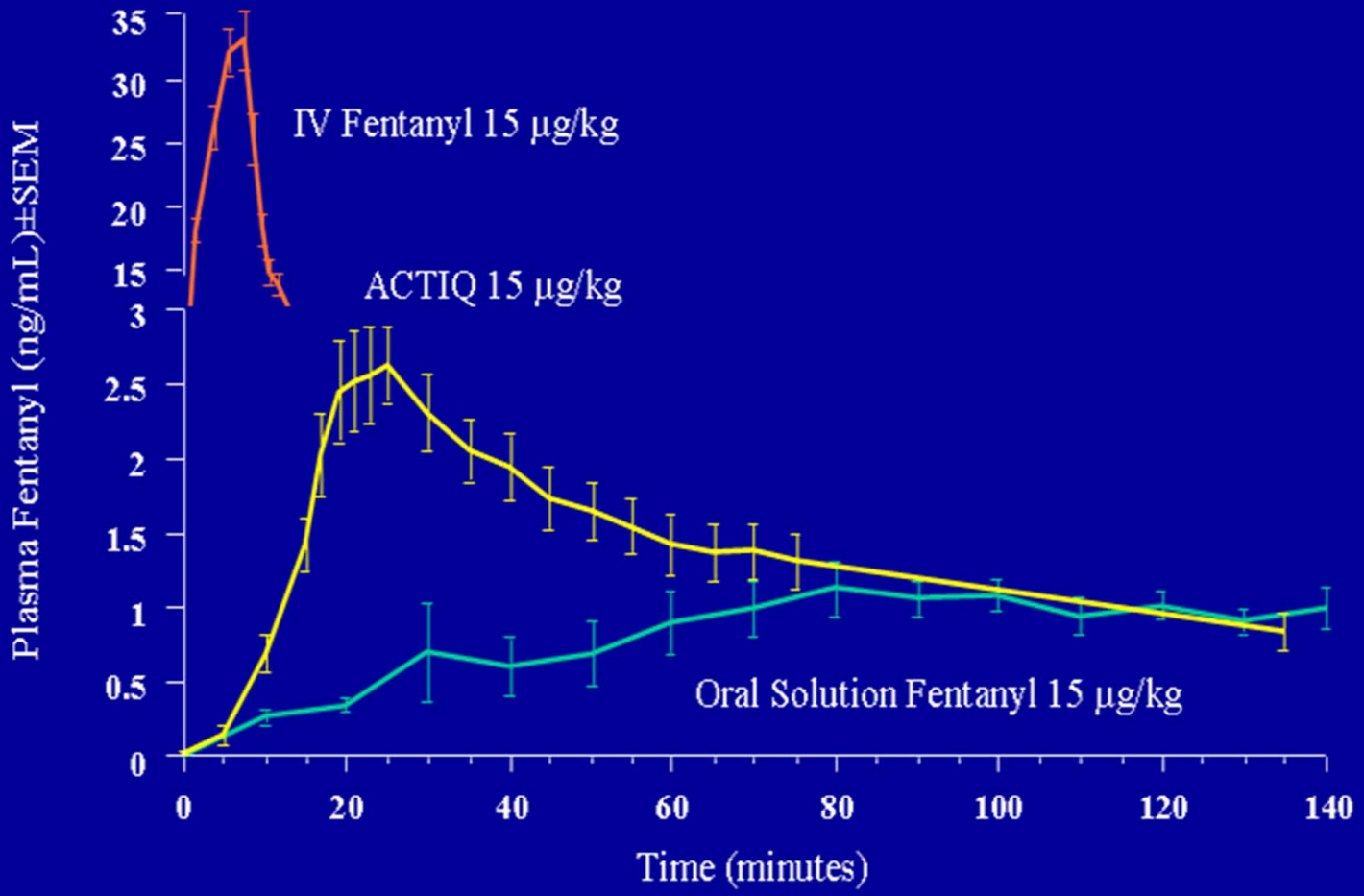
Attributes of ACTIQ

- 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



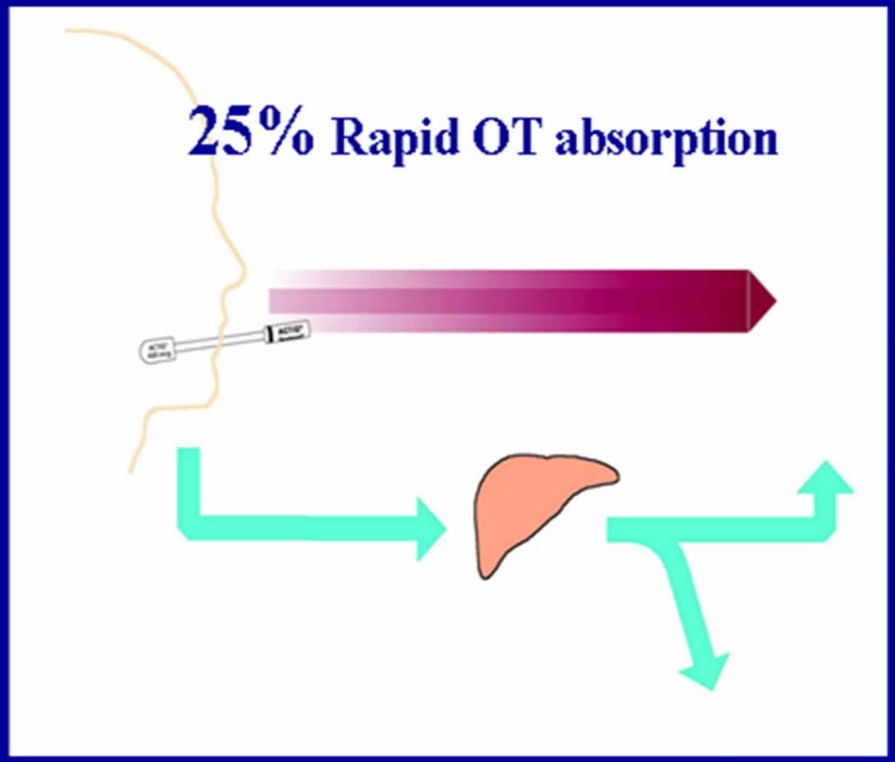
Adapted from Streisand JB, et al. *Anesthesiology*. 1991;75:223-229.

ACT 225

P-22551 _ 00010

Total Fentanyl Bioavailability Following ACTIQ Administration Is 50%

After standardized consumption time of 15 minutes*



50% Total bioavailability

- 25% Rapid OT absorption
- 25% Slow GI absorption
- 50% Lost to metabolism

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

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

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.

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.

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.

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.

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

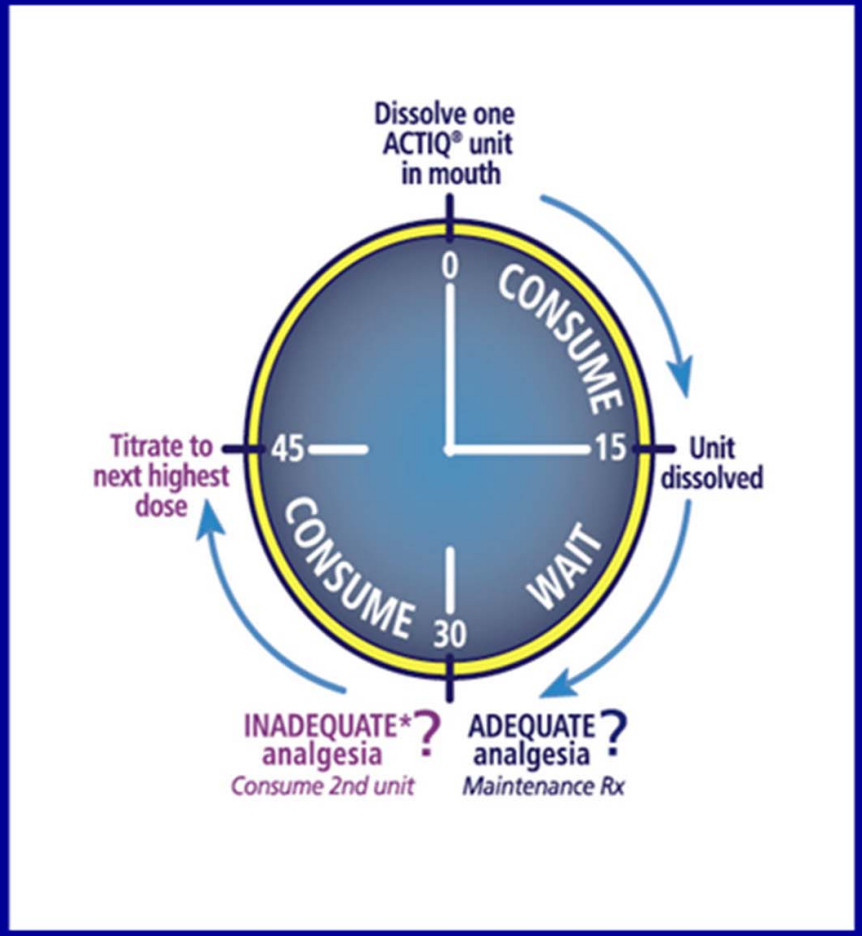
- Clock for 15 minutes – the recommended dosing time
- An ACTIQ unit should be completely finished in 15 minutes to get the most relief. If an ACTIQ unit is finished too quickly, more of the medication is swallowed and the patient will receive less relief

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)

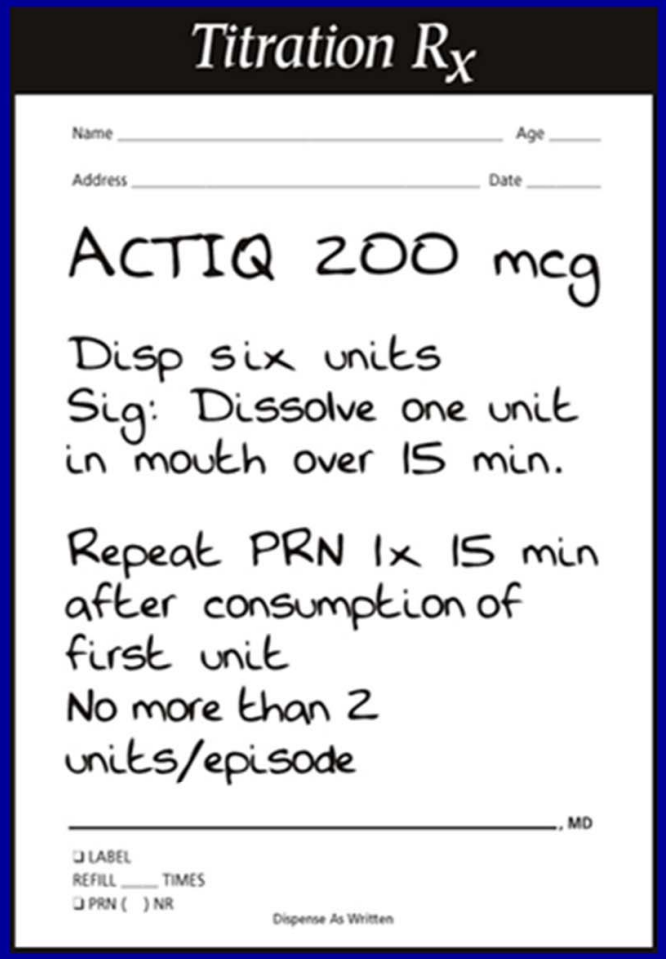
ACTIQ Titration Process

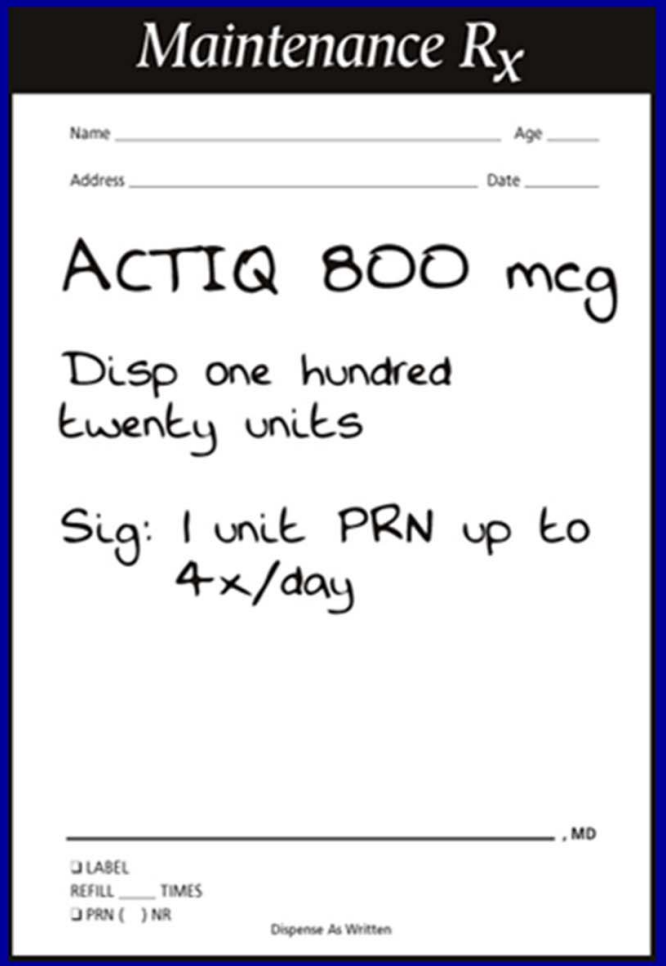


*If treatment of several consecutive breakthrough cancer pain episodes requires more than one ACTIQ unit per episode, return to top of diagram using next highest dosage strength.

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.

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.

References (cont.)

- 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.