

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**20-747/S003**

***Trade Name:*** Actiq

***Generic Name:*** Fentanyl citrate

***Sponsor:*** Anesta Corporation

***Approval Date:*** March 26, 1999

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-747/S003**

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<b>Reviews / Information Included in this NDA Review.</b>
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<b>Labeling</b>	
<b>REMS</b>	✓
<b>Summary Review</b>	
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<b>Office Director Memo</b>	
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<b>Proprietary Name Review(s)</b>	
<b>Administrative/Correspondence Document(s)</b>	✓

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-747/S003**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-747/S-003

Anesta Corporation  
4745 Wiley Post Way, Suite 650  
Salt Lake City, Utah 84116

MAR 26 1999

Attention: Patricia J. Richards  
Director, Regulatory Affairs

Dear Mrs. Richards:

Please refer to your supplemental New Drug Application (sNDA) dated February 10, 1999, received February 12, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Actiq (Oral transmucosal fentanyl citrate) 200 µg, 400 µg, 600 µg, 800 µg, 1200 µg, and 1600 µg.

We acknowledge receipt of your submissions dated February 26, 1999 and March 23, 1999.

The supplemental application provides for revisions to the Risk Management Plan that was approved in our letter of November 4, 1998.

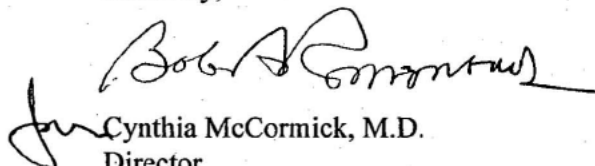
We have completed the review of this supplemental application, as amended, including the revised pricing plan, and it is approved.

For future reference, revisions to the RMP must be submitted as a supplement that requires our prior approval.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Nancy Chamberlin, Regulatory Project Manager, at (301) 827-7410.

Sincerely,



Cynthia McCormick, M.D.  
Director  
Division of Anesthetic, Critical Care, and  
Addiction Drug Product HFD-170  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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cc:

Original NDA 20-747

HFD-170/Div. files

HFD-103

HFD-170/Chamberlin/C.Moody

HFD-170/B.Rappaport/C.McCormick

HFD-170/Cortinovis/D'Sa/Doddapaneni

DISTRICT OFFICE

HFD-92/DDM-DIAB

HFD-40/DDMAC

HFD-820/ONDC

Drafted by: nc 3-24-99

Revised: 3-26-99 nc

Initialed by: C. P. Moody 3-26-99

final:

APPROVAL (AP)

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-747/S003**

**REMS**

**Actiq®**  
**(oral transmucosal fentanyl citrate)**

**Risk Management Program**

(February 9, 1999)

**NDA Number: 20-747**

**Sponsor:**

Anesta Corp.  
4745 Wiley Post Way  
Plaza 6, Suite 650  
Salt Lake City, UT 84116  
801.595.1405

**Marketing Partner:**

Abbott Laboratories  
Hospital Products Division  
Abbott Park, IL 60064

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## 1.0 Introduction

The *Actiq* Risk Management Program (RMP) has been designed to address three key potential risk situations:

1. accidental ingestion of *Actiq* by children
2. improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3. diversion or abuse

Anesta Corp. and Abbott Laboratories have designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible. This program includes the following:

- strong labeling for professionals, patients and caregivers
- product specific design features to increase child safety
- redundant child-resistant packaging and storage containers
- comprehensive professional, patient caregivers, and child educational programs
- interventions at the point of dispensing
- CII status for *Actiq*

This document provides details and implementation tactics for all elements of the *Actiq* Risk Management Program. No single element can provide the complete answer to reducing risk. A lengthy series of events must occur in sequence before a risk event can occur, yet any one of multiple RMP elements can intervene to interrupt the sequence and prevent the risk event. Redundancy of program elements is one measure used to strengthen the effectiveness of the RMP.

The purpose of the RMP is to ensure the safe use of this product. It is not intended that any portions of this RMP should be used in a promotional context or used to promote *Actiq* in a manner inconsistent with the product label.

The RMP and all of its components should be fully operational at the time of launch.

### 1.1 Key Messages for the RMP

There are several key messages repeated throughout the RMP, which are listed below. For the balance of the document, these messages will be referenced simply as Child Safety, Proper Patient Selection and Prevention of Diversion and Abuse messages.

- Child Safety Messages
  - *Actiq* must be kept out of the reach of children
  - *Actiq* could be harmful or fatal to a child if accidentally ingested

- *Actiq* must be properly stored and handled
- *Actiq* must be properly disposed of after use
- Healthcare professionals must counsel patients on child safety messages
- Accessible and easily understood directions on what to do in case of accidental ingestion
- Proper Patient Selection Messages
  - Definition of an opioid tolerant patient
  - *Actiq* is specifically contraindicated for use in opioid non-tolerant patients
  - *Actiq* is specifically contraindicated for use in acute/postoperative pain
  - Directions on what to do in case of suspected overdose
  - *Actiq* is specifically indicated solely for the treatment of breakthrough cancer pain in chronic opioid tolerant cancer patients
- Prevention of Diversion and Abuse Messages
  - *Actiq* is a CII medication
  - *Actiq* is to be used only by the patient for whom it is dispensed
  - *Actiq* may be habit forming
  - *Actiq* requires appropriate disposal of unused medication

## 2.0 Product Definition

The *Actiq* unit, containing dosages of fentanyl ranging from 200 to 1600 mcg per unit, consists of a raspberry-flavored lozenge on a handle (see Attachment 1). *Actiq* provides median peak fentanyl blood levels in 20-40 minutes (range of 20-480 minutes) when the unit is consumed over a 15-minute period and fentanyl is absorbed by a combination of transmucosal and gastrointestinal absorption.

Concern has been raised that *Actiq* may be perceived as a lollipop. Because of the design of the *Actiq* unit and its drug delivery characteristics, steps will be taken in an effort to minimize the risk of accidental poisoning, inappropriate use and diversion.

### 2.1 *Actiq* Unit

The *Actiq* unit consists of an opaque, white to off-white drug matrix that has been opacified and colored to make it look less appealing to children. Its handle has been designed with a "paddle" with a molded "Rx" in the center to identify it as a product for medical use. Additionally, on the back side of the paddle the word "fentanyl" is clearly visible.

The *Actiq* unit complies with current drug imprinting requirements (see 21 CFR §206.10, Imprinting of Solid Oral Dosage Form Products for Human Use). The handle carries legible, laser-engraved product identification information (ie, microgram content of active drug, product code, Abbott logo, and "fentanyl") in 9 point, charcoal-gray type on a pure

white background. The laser-engraved imprint on the handle is intended to provide immediate documentation of drug and dose in the event of an accidental poisoning.

## 2.2 . *Actiq* Child-Resistant Pouch

Each *Actiq* unit is individually sealed in its own child-resistant pouch. The *Actiq* pouch is made of a heavy, multi-layer laminated foil material and requires scissors to open. It meets the specifications provided in the Poison Prevention Packaging Act. The child-resistant testing was conducted in compliance with the Poison Prevention Packaging Act of 1970, 16 CFR §1700, cited in the Federal Register (Volume 38, No. 151, August 7, 1973). This package passed the child resistance test protocol with a 99% effectiveness rating, exceeding the 80% requirement.

Individual child-resistant packaging (one dosage unit in each pouch) is intended to minimize exposure by limiting access to just one unit at a time.

The pouch is opaque. A child cannot see the unit when it is in its pouch. The pouch does not resemble food or most candy wrappers.

The dosage strength of each unit is marked on each handle, and on the foil pouch and shelf carton. The colors are a secondary aid in product identification.

Gray	200 mcg
Blue	400 mcg
Orange	600 mcg
Purple	800 mcg
Green	1200 mcg
Burgundy	1600 mcg

The front of each pouch utilizes an icon to draw attention to warnings about child safety and opioid tolerance, standard product identification information is also included on the front of the pouch (see Attachment 2). The back of each pouch contains the same icon, plain-language warnings about child safety and proper product storage, and a reminder to read the *Actiq* Patient Leaflet.

The front of each pouch contains the CII symbol, a "May be habit forming" warning, and an "Rx only" warning.

## 2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Attachment 3). The shelf carton contains strong warnings prominently and redundantly displayed on the front and back pharmacy label space on the back of the shelf carton.

- The front of the shelf carton has a conspicuous icon calling attention to warnings about child safety, and a reminder to read the *Actiq* Patient Leaflet. There is also a warning about appropriate patient selection.
- The right hand side of the back of the shelf carton contains a designated location for the application of the pharmacy-dispensing label. A checklist for the pharmacist is included in this space. The checklist reminds the pharmacist to make sure the

patient is already taking opioids chronically, to counsel the patient about child safety, to encourage the patient to read the *Actiq* Patient Leaflet, to discuss the *Actiq* Welcome Kit, and to counsel the patient about disposal of partially consumed units.

- On the left hand side of the back of the shelf carton an icon calls attention to prominent warnings about child safety, the need for appropriate patient selection (opioid tolerance), the importance of appropriate disposal of partially consumed units, a reminder to read the *Actiq* Patient Leaflet, and prominent instructions on what to do in case of an accidental exposure.
- On the top of the shelf carton is another reminder for the patient or caregiver to read the *Actiq* Patient Leaflet.

At the initiation of *Actiq* therapy, it is recommended that physicians prescribe an initial supply of six 200 mcg units. At each new dose of *Actiq* during titration, it is recommended that only six units of the next higher dose be prescribed to limit the potential for left over units in the home.

The most prominent front panel warnings will be provided in Spanish in sticker form to pharmacies upon request. As additional languages are identified, appropriate stickers will be developed and distributed in a similar fashion.

Each shelf carton contains eight strips of three pouches, for a total of 24 pouches of a single strength of *Actiq*. The shelf carton represents approximately a ten day to two-week supply of *Actiq* after the appropriate dose has been established via titration. Except for the top panel, all printed panels of the shelf carton contain the CII symbol.

## 2.4 Potential Partially Consumed *Actiq* Units

It is important to limit the availability of unused and partially consumed units in the home. Warnings are placed on the shelf cartons to remind patients to properly dispose of partially consumed units. The following steps will be taken to reduce the availability of unused and partially consumed units by (1) the provision of multiple dosage strengths, (2) proportional pricing, and (3) directions for prescribing.

### 2.4.1 Multiple Dosage Strengths

*Actiq* will be made available in six dosage strengths (200, 400, 600, 800, 1200, 1600 mcg units) so that patients can be titrated to the unit strength which provides adequate relief with acceptable side effects. The directions to both healthcare professionals and patients clearly state that *Actiq* dosage units *are to be completely consumed*.

### 2.4.2 Pricing

Pricing of *Actiq* will provide proportionality on a per mcg basis. This pricing plan is an attempt to minimize the economic incentive to partially consume an *Actiq* unit and save the remainder for a future breakthrough cancer pain episode, reducing the potential risk to children.

### 2.4.3 Prescribing Directions

As per the *Actiq* titration instructions, the initial recommended prescription size is six units of the 200 mcg dose. If a patient requires a higher dose, the titration instructions recommend a second prescription of six units of the 400 mcg dose. This process of prescribing six units of the next highest available dosage form is recommended until the appropriate dose is found.

The package insert contains specific instructions recommending that physicians prescribe a small quantity (6 units) for titration and/or dosage adjustment in an effort to minimize the number of units in the home.

## 3.0 Labeling

### 3.1 CII (Schedule II Classification)

The U.S. Drug Enforcement Administration places very specific controls on the storage, distribution, accountability, prescribing and usage of scheduled products (see 21 CFR §1301). *Actiq* will be a CII product, consistent with other strong opioids such as fentanyl, morphine, oxycodone, and hydromorphone-based products. CII is the most restrictive classification available, and raises the overall level of vigilance and surveillance by all parties involved with the product. These restrictions include:

- strongest tracking and controls throughout the distribution system (DEA Form 222 required for all transactions)
- strict accountability of finished units
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to check for a legitimate medical purpose before dispensing

The status of *Actiq* as a CII product is the primary risk management element against the third potential risk event -- the potential for diversion and/or abuse. It is important to note, however, that simply the fact that a product is CII raises the level of attention devoted to the prescribing and dispensing of the product by all parties involved in the process and that this is expected to also reduce the risk of accidental ingestion and prescribing for opioid non-tolerant patients because of this heightened awareness.

### 3.2 Patient Leaflet

A Patient Leaflet has been written for *Actiq*, and four copies will be packaged in every shelf carton (see Attachment 4). Extra copies will be broadly distributed for use by physicians, nurses, pharmacists, caregivers, and patients. The leaflet will be included in the *Actiq* Welcome Kit and in other direct to patient communication and educational programs. It will be available in Spanish as well.

- The first page of the *Actiq* Patient Leaflet contains a strong boxed warning and redundant child warning with graphics for emphasis.

- The *Actiq* Patient Leaflet explicitly addresses, in plain language, preventing access by children. These messages include:
  - Child Safety messages
  - safe storage instructions for whole and partially consumed units
  - Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized “walk through” of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.
  - a prompt to call 911 if the patient or child is not awake and alert
  - a prompt to call Poison Control at 1-800-690-3924 if the patient or child is awake
  - instructions for care of the patient or child who is having trouble breathing or not breathing at all
- It contains proper patient selection messages
- Strong language has been used throughout the *Actiq* Patient Leaflet. In all warning statements, the word “must” is used instead of the word “should.” The warning language “can be harmful or fatal to a child” and “can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines...” is used.

### 3.3 Package Insert

The *Actiq* Package Insert (PI) clearly and explicitly communicates messages about child safety, proper patient selection, and prevention of diversion and abuse (see Attachment 5). These messages (see Attachment 6) are important elements of the RMP. The PI highlights the serious risks associated with *Actiq* use and mandates that the healthcare professional must become involved in the process of educating patients and home caregivers. The key elements in the PI include:

- 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.
- Black box warnings, which are:

**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 non-tolerant 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.**

- Titration instructions which minimize the number of units in the home
- Detailed safe home handling and storage
- Detailed instructions for disposal of used and unused units
- CII designation

#### **4.0 Professional Medical Education**

Anesta and Abbott will work in conjunction with FDA (through the Office of Health Affairs) in interfacing with licensing boards and professional associations on the development of and dissemination of educational materials related to *Actiq*.

##### **4.1 Key Message Points**

The education of physicians, nurses, pharmacists, caregivers and patients on the safe use of *Actiq* is an integral part of the *Actiq* Risk Management Program. These educational messages are drawn directly from the *Actiq* Package Insert. The key safety messages, which have been described earlier in section 1.1 of this RMP, include:

- Child safety messages
- Proper patient selection messages
- Prevention of diversion and abuse messages

The educational programs for physicians, nurses, pharmacists, caregivers and patients will also reinforce the following:

- Process for titration to an effective dose
- Proper (total) consumption of the product
- Proper storage and disposal of the product

- Efficacy and side effects of the product
- Basic Life Support training and potential for certain families to be trained in the treatment of accidental narcotic overdose including antagonist therapy.

These key educational messages, primarily focusing on safety, will be provided to the physicians, nurses and pharmacists through the communication vehicles, which are discussed on the following pages.

#### **4.2 Breakthrough Cancer Pain Nursing Medical Education Monograph**

This monograph is written by nurses who participated in the *Actiq* clinical trials. It contains specific information about breakthrough cancer pain and the *Actiq* key safety messages. It will be distributed via direct mail and the sales force. This publication has also received Oncology Nursing Society CEU certification for 3.5 hours of continuing education. This as well as all educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

#### **4.3 The *Actiq* Speakers Bureau / Medical Education Programs**

Prior to product launch, Anesta and Abbott will formally train the following professionals on all aspects of *Actiq* consistent with the package insert, particularly the RMP elements (Attachment 6):

- At least 50 prominent physician educators in pain management
- At least 50 prominent nurse educators in pain management
- At least 25 prominent pharmacist educators in pain management

These groups will then be called upon to educate their respective peers and patients via presentations in local, state, regional, and national settings.

#### **4.4 Publications**

Manuscripts will be submitted to peer-reviewed journals for consideration. They will include messages that reinforce elements of this RMP. The manuscripts selected for publication are those that combine a specific focus into the key cancer pain management audience, as well as other healthcare groups who make up the RMP target audience.

##### **4.4.1 Broad-Based Publications**

- Journal of the National Cancer Institute (circulation 10,000+)
- Journal of Pain and Symptom Management (circulation 10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)

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- Journal of Hospice and Palliative Care (circulation 3,000)
- Oncology Times (circulation 20,000)
- Cancer for the Clinician (circulation 10,000)

#### 4.4.2 Pharmaceutical Compendia

Pharmaceutical compendia will serve physicians, nurses, and pharmacists in several ways. The compendia regularly send out updates to inform about new products. The circulation numbers for each of these publications, although proprietary, are believed to be greater than 50,000 per publication. Abbott and Anesta will have *Actiq* listed in each of the following well-known compendia:

- Physician's Desk Reference (PDR)
- American Hospital Formulary Service (AHFS)
- Facts and Comparisons

In cases where material is excerpted from the Package Insert, Anesta will contact these publications to request increased emphasis on the RMP elements.

#### 4.4.3 Major Nursing Journals

- American Journal of Nursing (circulation 250,000+)
- American Journal of Hospice and Palliative Care (circulation 100,000+)
- Nurse Practitioner (circulation 100,000+)
- Home Health Care Nurse (circulation 25,000+)
- Clinical Journal of Oncology Nursing (circulation 20,000+)
- Seminars in Oncology Nursing (circulation 6,000+)
- Oncology Nursing Forum (circulation 20,000+)
- RN Magazine (circulation 200,000+)

#### 4.4.4 Cancer and Nursing Professional Society Newsletters

- The Oncology Nursing Society Newsletter
- Local ONS chapter newsletters
- Oncology Nursing Society computer mail announcements
- State board of nursing newsletters
- State Cancer Pain Initiative mailings

#### 4.4.5 Major Pharmacy Journals

- U.S. Pharmacist (circulation 100,000+)
- Drug Topics /Hospital Pharmacist's Report (circulation 100,000+)

- Formulary (circulation 100,000+)
- Journal of the Association of Healthsystem Pharmacists (circulation 70,000+)
- Journal of the American Pharmaceutical Association (circulation 48,000+)
- Journal of Managed Care Pharmacy (circulation 40,000+)

#### 4.4.6 Pharmacy Newsletters (Print and Electronic)

Abbott and Anesta will request that the *Actiq* key safety messages and new product reviews be incorporated into the newsletters of various national, regional, state and local pharmacy organizations including:

- The Pharmacist's Letter (circulation - 100,000+)
- Chain drugstore newsletters and electronic updates
  - CVS 4,000 stores
  - RiteAid 3,000 stores
  - Walgreens 2,200 stores
- State board of pharmacy newsletters

#### 4.5 Communication with DEA

Information on proper disposal of *Actiq* will be provided to the DEA for use by their field offices on an as requested basis. Background and training materials will be designed in concert with the Office of Diversion Control, Policy Liaison at DEA headquarters and will be distributed to all DEA field offices.

#### 5.0 *Actiq* Launch Program

*Actiq* will target a relatively small group of clinicians. The emphasis of the promotion will be highly educational.

All educational and promotional launch materials will be submitted to and reviewed by FDA prior to use.

## 5.1 Target Audience

The target physician audience for *Actiq* is a group of approximately 5,000 oncologists and pain specialists, their nurses and office staff. These physicians are already using CII opioids to treat cancer pain, are generally knowledgeable about breakthrough cancer pain, and should understand the appropriate use of *Actiq* for opioid tolerant cancer patients.

Since the majority of *Actiq* use is anticipated to be in the oncology outpatient setting, the pharmacist will play an important gate keeping role in the *Actiq* RMP by screening for proper patient selection (opioid tolerant cancer patients only) and by providing information on safe product use and handling to patients and caregivers.

Please note the entire universe of practicing oncologists, oncology nurses and pharmacists will receive the key messages through some of the broad-based communication vehicles described in the Professional Education section of this document.

## 5.2 The Oncology Specialist (Abbott Sales Organization)

Approximately 40 full time Oncology Specialists will be placed in the field to personally call on the target audience. The Oncology Specialists will be the primary day to day link to the physicians, nurses and pharmacists who will be using the product. The Oncology Specialists will play a key role in implementing the RMP.

Each Oncology Specialist must be certified on *Actiq* via a rigorous product education and sales training program. This program begins with four home-study modules, which explicitly spell out the three groups of key safety messages. The home study modules are followed by two weeks of in-house training at Abbott corporate headquarters and at least one week of training in the field with a field trainer or seasoned field manager. This program is designed to clearly communicate the key safety messages and Abbott expectations regarding sales activity in the field. Importantly, Oncology Specialists will be tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the Oncology Specialists will personally call on 1,000 of the 2,000 pharmacies dispensing the largest volume of CII products. In these calls they will educate the pharmacist on all safety issues and enlist their assistance as gatekeepers. The second group of 1,000 high CII dispensing pharmacies will be called on by the Oncology Specialist in the first three months post product launch with the same messages.

Pharmacies not included in the initial target group will be offered opportunities to obtain additional information through several elements of the *Actiq* Risk Management Program, including: Dear Pharmacist letter, pharmacy direct mail services, pharmacy journal advertising, pharmacy newsletters, and pharmaceutical compendia. These programs will provide access to the 1-800 number and website for additional information about *Actiq*. In addition, the group of pharmacies and health care practitioners serving rural areas will be the target of a post approval commitment to better understand and meet their unique needs through an educational outreach program.

Upon hiring, each Specialist will receive a letter outlining his responsibilities. This letter will stress the requirement to limit the promotion of *Actiq* to the approved indication, discourage off-label use, direct the specialist to promote only to the target audiences, describe the serious consequences of violating this policy, and reinforce the three key messages of the RMP. The letter must have FDA review and prior approval before issue. Moreover, the compensation program for Oncology Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the Oncology Specialist will discuss a variety of educational material which may include:

- Package insert and patient leaflet
- *Actiq* safety video
- *Actiq* CD-ROM programs for physicians, nurses, and pharmacists
- *Actiq* Internet site
- Central 1-800 poison control number
- The *Actiq* Welcome Kit

All materials will be submitted to and reviewed by FDA prior to use.

### 5.3 Detail Aids

Detail aids for *Actiq* will emphasize the three key safety messages. To ensure consistent attention to the key safety messages, all "leave behind" detail aids will also prominently display the detail flag. This flag as well as all other promotional materials will be submitted to and reviewed by FDA prior to use.

### 5.4 Direct Mail

All materials will be submitted to and reviewed by FDA prior to use.

#### 5.4.1 *Actiq* Professional Information Kit

Upon product launch, the target physician group will receive an *Actiq* Information Kit including:

- *Actiq* Package Insert and *Actiq* Patient Leaflet
- *Actiq* Safety video designed for patients which covers
  - child safety
  - patient selection (opioid tolerance)
  - titration
  - storage
  - disposal
  - emergency care
- Information on accessing the 1-800 number, the *Actiq* internet site and Physician CD-ROM program all of which are designed to provide additional information
- Information on how to obtain the *Actiq* Welcome Kit

#### 5.4.2 The Dear Doctor Letter

Upon product approval, a mass mailing to registered physicians in the U.S. will be conducted. This letter will reinforce the three key messages (child safety, proper patient selection and prevention of diversion and abuse) and encourage the appropriate physicians to mail in an enclosed business reply card and/or to visit the *Actiq* internet site for more information. The letter must have FDA review and prior approval before issue.

#### 5.4.3 The Dear Pharmacist Letter

Upon product approval, a mass mailing to registered pharmacists in the U.S. will be conducted. The letter must have FDA review and prior approval before issue. This letter will reinforce proper patient selection and child safety messages and encourage the pharmacists to mail in the enclosed business reply card and/or visit the *Actiq* internet site for more detailed information.

#### 5.4.4 Pharmacy Direct Mail Services

Information to pharmacists using pharmacy direct mail services will prominently feature the three key safety messages. All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

### 5.5 Multimedia Programs

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

#### 5.5.1 *Actiq* CD-ROM Program

A CD-ROM will be developed and made available to all *Actiq* target audiences. It will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. A detailed schematic of the separate CD-ROM programs for physicians, nurses, and pharmacists is presented in Attachment 7. This program will be available via mass direct mail, the Oncology Specialist and the *Actiq* internet site.

#### 5.5.2 *Actiq* Internet Site

An *Actiq* internet site will be made available to all *Actiq* target audiences. This will include discussions of child safety, proper patient selection, prevention of diversion and abuse, appropriate product usage, product handling, storage, and disposal. Sections will be targeted at physicians, nurses, pharmacists, patients and caregivers.

#### 5.5.3 Emergency 911

This number will be prominently featured in all patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the person (eg, a child) is not awake and alert or is breathing slowly.

### 5.5.4 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established at the Rocky Mountain Poison Control Center to receive all US emergency calls for *Actiq*. Having a central number allows for a focused, well-trained staff to be able to deliver a consistent message to patients and caregivers. It also provides for a near real-time surveillance of all poison control calls and an opportunity for timely analysis of any trends. This number will be prominently featured in patient educational materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the person (eg, a child) is awake and alert.

## 6.0 Patient and Caregiver Education

### 6.1 The *Actiq* Welcome Kit

Upon launch, the 5,000 target oncologists and pain specialists will receive a supply of the *Actiq* Welcome Kit. The *Actiq* Welcome Kit will include the following items:

- Child Safety Lock - a lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Attachment 8).
- Secure Personal Container - a lockable pouch with a waistband (a fanny pack) will be provided so the patient can safely and conveniently store a day or two supply of *Actiq*. This pouch can be secured directly to the patient or to patient's bed or chair (Attachment 9).
- Child-Resistant Temporary Storage Container - an opaque container featuring easy-entry, but child-resistant removal. A warning decal will be attached to the outside of each container. This bottle will fit into the secure personal container (fanny pack) and will be used to secure completely and/or partially used *Actiq* units (should they exist) until the patient or caregiver can properly dispose of them (Attachment 10). Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.
- Patient Leaflet
- Home Warning Stickers and Magnet (detail in section 6.3)
- Children's Booklet (detail in section 6.4)
- Emergency treatment information
- A brightly colored flyer with a special alert to families with young children

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

Every *Actiq* patient will receive a free Welcome Kit from his or her physician or via a 1-800 number. The kit and ordering information for it are described in the Patient Leaflet. Target pharmacists will be given an *Actiq* Welcome Kit by an Oncology Specialist and briefed on how patients can obtain them.

Several components of the Welcome Kit--the Patient Leaflet and the Child Safety booklet -- will be available in Spanish, and will be distributed in those geographical areas with high Hispanic populations. These will be available on request through the 1-800 number.



## 6.2 Patient Oriented *Actiq* Safety Video

A detailed patient oriented safety video will be made available to practitioners and patients to communicate the following messages:

- Child safety messages
- Proper patient selection messages
- Product storage and handling in the home
- Product titration
- Product disposal
- Emergency instructions

This video will be mailed to the offices of the target physicians and will also be available to physicians and patients through the Oncology Specialist or 1-800 number. This video will be available in either English or Spanish.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

## 6.3 Home Warning Sticker / Refrigerator Magnet

An *Actiq* specific home warning sticker and refrigerator magnet will be distributed to all *Actiq* patients through the *Actiq* Welcome Kit. This sticker/magnet is to be placed around the home in high visibility areas and on the telephone. They will provide warnings for child safety and proper patient selection and contain emergency instructions for calling 911 and the central 1-800 poison control number.

## 6.4 Children's Booklet

A child-friendly booklet designed by the National SAFEKIDS Campaign in collaboration with the chairperson of the public education committee of the American Association of Poison Control Centers, Gail Banach, M.S.Ed., to be read and to be understood by younger children will be distributed. This book has been developed at a 2nd to 4th grade reading level. Older children may read it on their own. The primary goal of this booklet is to educate children on safe handling of all medicines including *Actiq*. The booklet will use simplistic language, realistic graphics and will be interactive to maximize the child's learning. This booklet will be made available in English or Spanish in the *Actiq* Welcome Kit and in the offices of all target physicians and pharmacists.

All content will be submitted to and reviewed by FDA (DDMAC) prior to use.

## 7.0 Point Of Dispensing Interventions

The following activities will be implemented at the *Actiq* points of dispensing. Product samples will not be made available.

### 7.1 Pharmacy Software Systems - Precaution Software

In order to prompt the pharmacist to inquire about the presence of children in the home and to verify opioid tolerance of the patient, vendors of major commercial pharmacy precaution software will be asked to place *Actiq* warnings in their systems being used in the U.S. and its territories. Participating software systems will cover approximately 90% of the data systems in the U.S. pharmacy market.

Examples of pharmacy warning screens and electronically produced patient information sheets are provided as Attachment 11.

## 7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an Oncology Specialist and will be made available to any pharmacist upon request. The pharmacist will be encouraged to explain to the patient how they can obtain a free *Actiq* Welcome Kit, if they do not already have one, either directly from their physician or via a 1-800 number. Directions to obtain the *Actiq* Welcome Kit are also provided in the Patient Leaflet.

In addition to being enclosed in each *Actiq* shelf carton, the Patient Leaflet will be distributed in quantity to all target pharmacists by the Abbott Oncology Specialists and be made available to any pharmacist upon request. The package (eg, back panel of shelf carton) and the computer program screen will prompt the pharmacist to go over the *Actiq* Patient Leaflet with every new *Actiq* patient. The Patient Leaflet will also be provided in the *Actiq* Welcome Kit. Where possible (eg, the *Actiq* Internet site and CD-ROM), the *Actiq* Patient Leaflet will be made available electronically.

## 7.3 Temporary Storage Container

Temporary storage containers will be available at the point of dispensing whenever and wherever *Actiq* is dispensed.

## 8.0 Surveillance Goals And Activities

The goals of the *Actiq* Surveillance and Monitoring Program are to:

- determine the effectiveness of the *Actiq* Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, off-label use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the *Actiq* Risk Management Program to improve its effectiveness

The following pages summarize the various means by which *Actiq* use and safety data will be collated and analyzed. (In the event that any of these pharmacy organizations are unable to participate in this program, Abbott/Anesta will commit to substituting another potential supplier to broaden our sample in a timely manner.)

## 8.1 Direct Patient Feedback

### 8.1.1 Chain Pharmacy Call Back System

A call back system will be used to directly query *Actiq* patients. Under this program, patients who receive an *Actiq* prescription at a participating pharmacy will receive a follow-up phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an *Actiq* Welcome Kit?
- Was the patient already on a strong opioid when they received the *Actiq* prescription?
- Was the patient or caregiver provided with the appropriate safety messages?
- What titration process has been used to this point?
- Are there any children in the home or with access to the home?
- How is the patient or caregiver storing and disposing of the product?
- Provide a child safety reminder.

The partners included in this system include RiteAid, Eckerd, Walgreens, and the Merck Medco system. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill *Actiq* prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as Walgreen, RiteAid and Eckerd stores are well-distributed throughout the country, and the Merck Medco mail order system is one of the largest in the U.S.

After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

## 8.2 Prescription Monitoring

### 8.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of this data will be IMS Xponent, the largest sample available of *Actiq* prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents prescriptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. These data provide the prescriber's name, the physician specialty and zip code. These data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). Abbott will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

### 8.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. An example of an NDTI data sheet is attached (see Attachment 12). These data will be reported to the FDA on a quarterly basis as described in section 10.0.

### 8.2.3 Wholesaler Data

Per the FDA's previous agreement with Abbott Laboratories, *Actiq* will not be sold directly to retail pharmacy outlets, but will be sold only to DEA hospital and distribution registrants.

Abbott will receive information on retail pharmacy sales. This information will be shared with the Oncology Specialist. The Oncology Specialist will follow-up with these pharmacies to ensure that they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months an Abbott Trade Sales Specialist (wholesaler representative) will call on the high volume *Actiq* wholesalers. This person will request information on any additional pharmacies which need to be added to the list. Information from the Abbott Trade Specialists' meetings with wholesalers will be shared with the Oncology Specialists for follow-up.

The sponsor will monitor for compliance to the RMP "Point of Dispensing" and report violations to the FDA quarterly along with any interventions made as a result.

## 8.3 Adverse Events

### 8.3.1 Abbott Standard Operating Procedure

Abbott has established specific procedures to respond to serious adverse events, which may be associated with *Actiq*.

A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day. Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated.

Any adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by Abbott. The details of this procedure are summarized below.

- a) The incident report is reviewed by an investigation team, and an investigation is initiated. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.
- b) The medical experience analyst assigned contacts the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.
- c) The medical investigation conclusions are discussed with Anesta to determine reportability.

### 8.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type of adverse experiences will also be reported to the FDA within 15 days:

- Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of diversion (ie, use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."
- Any serious adverse drug experience which is determined to occur in the context of "off label use" (ie, that is used outside of the approved indication for *Actiq*) whether or not the experience is unexpected, will be processed and reported to the FDA as a "15 day Alert."

Definitions of "serious adverse drug experiences," "adverse drug experience," "unexpected adverse drug experiences," and "15-day Alert report," are stated in 21 CFR §314.80. These Special Safety commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (eg, call-in, literature, poison control centers, etc).

### 8.3.3 Literature Monitoring

In addition to specific event reporting, Abbott maintains a system to monitor the literature for adverse events. This review is conducted monthly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

## 8.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

### 8.4.1 Central 1-800 Poison Control Number

A single 1-800 telephone number will be established to receive emergency calls when *Actiq* has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poison control calls. This number will be highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

### 8.4.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. These data are available once yearly and will be included in the analysis for FDA quarterly reports.

## **8.5 Abuse**

Quarterly reports to FDA will include information, trends, and interventions derived from the following sources:

### **8.5.1 Routine Abbott Interaction with DEA**

Abbott Laboratories Corporate Regulatory Affairs maintains a proactive program to identify possible product diversion. Abbott routinely visits DEA District offices with jurisdiction over Abbott distribution facilities to review information on the potential "street use" of Abbott products. In addition, an interactive relationship has been developed so that Abbott is alerted to specific instances. Abbott will cooperate with DEA and state drug control authorities' investigations, as requested.

### **8.5.2 Abbott Exceptions System**

*Actiq* will be added to Abbott's exception reporting system to the DEA. Under this system, any orders that exceed the norm by two or more standard deviations are reported to the DEA for follow-up and investigation.

### **8.5.3 Drug Abuse Warning Network (DAWN)**

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

### **8.5.4 State Drug Control Authorities or State Boards of Pharmacy**

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.

## 8.6 Promotional Message Audit

Promotional message testing at six month intervals following product launch will be conducted to ensure that Oncology Specialists are accurately delivering the key safety messages. This will be accomplished via telephone interviews or paper questionnaires with physicians that are prescribing *Actiq* and have been called on by the Oncology Specialist. Where necessary, sales representatives will be re-trained and/or disciplined to ensure compliance with the targeted, focused launch/promotional plan.

## 9.0 Intervention

### 9.1 Off-Label Usage

#### 9.1.1 Individual Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

- 1) A letter from Abbott's Medical Department will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA review and approval before it is issued.
- 2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an Oncology Specialist will visit the physician/s to gather information and remind them of appropriate prescribing of *Actiq*.

#### 9.1.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed *Actiq* inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly *Actiq* prescriptions, Abbott will contact the appropriate professional society (ie, American College of Surgeons, American Society of Anesthesiologists). This letter will outline prescribing concerns and offer to implement an educational program in conjunction with the professional society in a national setting.

Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total *Actiq* prescriptions for two additional quarters, an aggressive educational program will be initiated by mail clearly warning of the potential liabilities of prescribing *Actiq* to inappropriate patient populations.

### 9.2 Accidental Ingestion

In the event of an unintended pediatric exposure, Abbott will initiate their standard operating procedure for adverse events detailed in section 8.3.1 of this RMP.

## 10.0 FDA Reporting

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day Alert reports (see Section 8.3.2, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these 15-day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and the Division of Anesthetic, Critical Care, and Addiction Drug Products.

Anesta/Abbott will provide a quarterly report to the FDA compiled from all data collected by the methods described under the *Actiq* Surveillance and Monitoring Program and Interventions (see Sections 8.0 and 9.0 of this document). This report will describe and provide data on any concerns for child safety, diversion, and off-label usage. Anesta/Abbott will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the *Actiq* Risk Management Plan. This report will be provided as part of the *Actiq* quarterly report to the NDA during the first year of marketing. The sponsor and FDA will then determine requirements for further reports and their frequency after the first year of marketing. These reports will be cumulative and contain current reports and identified safety trends.

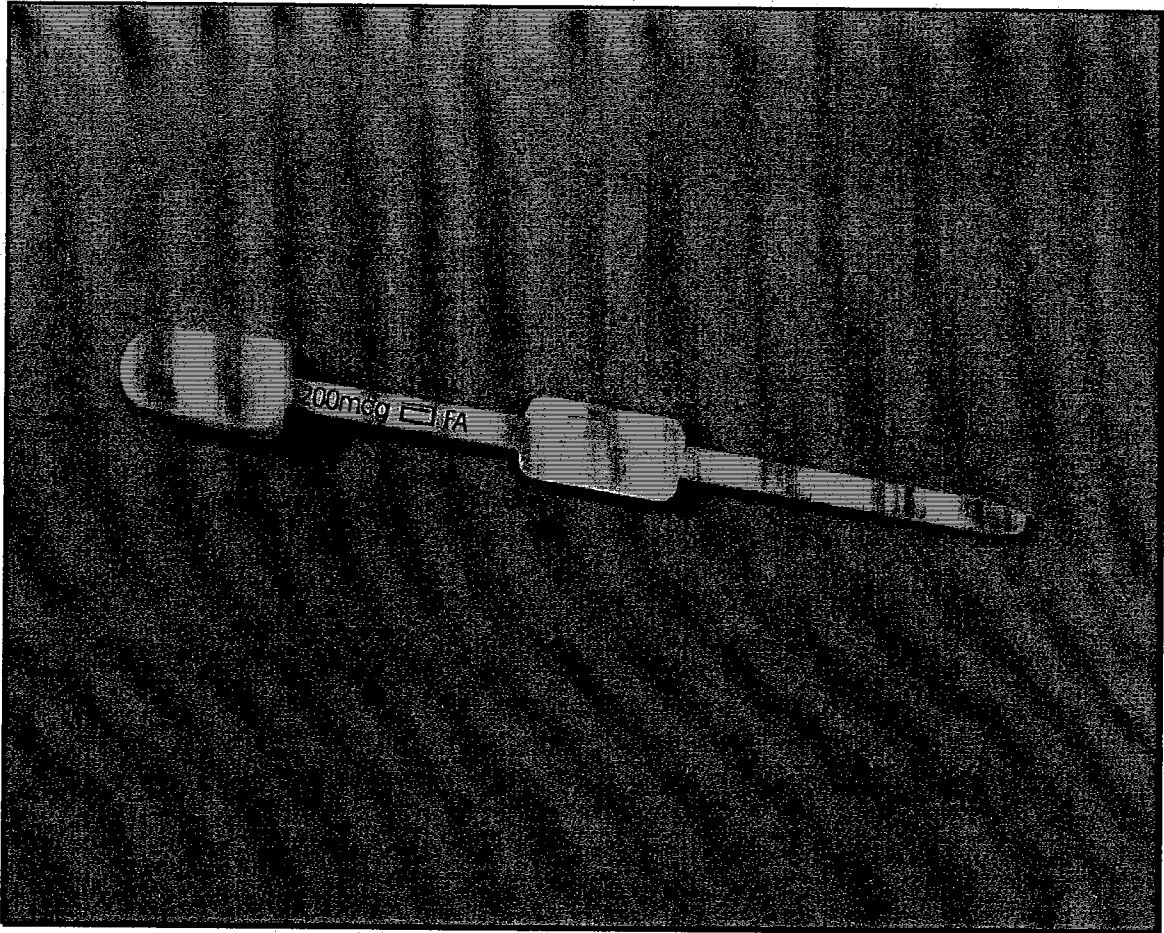


## List of Attachments

- 1     *Actiq* Dosage Unit (example: 200 mcg)
- 2     Labeling - Foil Pouch (example: 400 mcg)
- 3     Labeling - Shelf Carton (example: 400 mcg)
- 4     *Actiq* Patient Leaflet
- 5     *Actiq* Package Insert
- 6     Elements of RMP to be Included in Speaker Bureau Training
- 7     *Actiq* CD-ROM Schematic
- 8     Child Safety Lock
- 9     Secure Personal Container (ie, "fanny pack")
- 10    Child-resistant Temporary Storage Container
- 11    Pharmacy Computer Warning screens
- 12    IMS National Disease and Therapeutic Index example page

**Attachment 1**  
***Actiq* Dosage Unit**

*Actiq* Dosage Unit (example: 200mcg)




## **Attachment 2**

### **Labeling - Foil Pouch (example: 400 mcg)**


Labeling – Foil Pouch (example: 400 mcg)

Front Label

 Only for patients already taking opioids (narcotics) such as fentanyl or morphine 1 Unit/NDC 0074-2461-24

**ACTIQ<sup>®</sup>**  
(oral transmucosal fentanyl citrate)

equivalent to  
**400 mcg**  
fentanyl base




USE SCISSORS TO OPEN

**Warning: May be habit forming.**  
Each drug matrix contains fentanyl citrate equivalent to 400 mcg fentanyl base, sucrose, liquid glucose, artificial raspberry flavor and white dispersion G.B. dye. For oral transmucosal administration. See insert for dosage and administration. Store at 25°C (77°F) with excursions permitted between 15° and 30°C (59° and 86°F) until ready to use. (See USP Controlled Room Temperature.)


**Rx only**

Manufactured by: Abbott Laboratories, North Chicago, IL 60064, USA  
Distributed by: Abbott Laboratories, Inc., North Chicago, IL 60064, USA  
Under license from Anesta Corp., Salt Lake City, UT 84116, USA

 **WARNING: Keep out of the reach of children.**  
Accidental ingestion of this medicine by a child could be harmful or fatal.

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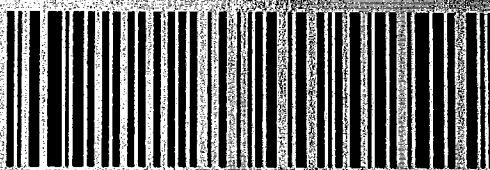
Back Label

 **WARNING: Keep out of the reach of children.**

- Store in locked cabinet out of the reach of children.
- Do NOT open this pouch until ready to use *Actiq*.
- Do NOT leave *Actiq* where a child could get it.

Read *Actiq* Patient Leaflet for important warnings and directions.

EXP LOT



(01) 0 030074 246124 5

## **Attachment 3**

### **Labeling - Shelf Carton (example: 400 mcg)**

Labeling- Shelf Carton (example: 400 mcg)

Front Panel

 24 Units  
Only for patients already taking opioids (narcotics) such as fentanyl or morphine

NDC 0074-2461-24

**ACTIQ<sup>®</sup>**  
(oral transmucosal  
fentanyl citrate)



equivalent to  
**400 mcg**  
fentanyl base

Warning: May be habit forming.

 **WARNING: Keep out of the reach of children.**  
Accidental ingestion of this medicine by a child could be harmful or fatal.  
Read enclosed *Actiq* Patient Leaflet for important warnings and directions.


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1 of 3


Labeling- Shelf Carton (example: 400 mcg)

Back Panel

**ACTIQ**  
oral transmucosal fentanyl citrate  
**400 mcg**



**Only for patients already taking opioids (narcotics) such as fentanyl or morphine**



**WARNING:** Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.

Partially consumed *Actiq* must be disposed of properly.

Read enclosed *Actiq* Patient Leaflet for important warnings and directions.

**To the Pharmacist:** Before dispensing *Actiq*, please do the following:

- ☐ make sure the patient is taking opioids chronically
- ☐ counsel the patient about child safety
- ☐ encourage the patient to read the *Actiq* Patient Leaflet
- ☐ discuss the *Actiq* Welcome Kit
- ☐ counsel the patient about disposal of partially consumed units

Place pharmacy label above


**What to do if a child or an adult accidentally takes *Actiq***

*Actiq* contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed *Actiq*. In these people, *Actiq* can cause their breathing to slow down or even stop. If you think someone has accidentally taken *Actiq*, follow these steps immediately:

1. Remove the *Actiq* unit from the person's mouth.
2. If the person is asleep, keep them awake by calling their name and shaking their arm or shoulder.
3. If the person is not awake and alert, call 911 or call for emergency help.
4. If the person is awake and alert, call Poison Control at 1-800-690-3326.

**While waiting for emergency help:**

4. If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.
5. If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.





1 030074 246124 2



Labeling- Shelf Carton (example: 400 mcg)

Left Side Panel

 24 Units

**ACTIQ<sup>®</sup>**   
(oral transmucosal  
fentanyl citrate)

equivalent to  
**400 mcg**  
fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 400 mcg fentanyl base, sucrose, liquid glucose, artificial raspberry flavor, and white dispersion G.B. dye.

For oral transmucosal administration. See insert for dosage and administration.

Store at 25°C (77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

**Rx only**

Right Side Panel

 24 Units

**ACTIQ<sup>®</sup>**   
(oral transmucosal  
fentanyl citrate)

equivalent to  
**400 mcg**  
fentanyl base

Manufactured by  
Abbott Laboratories  
North Chicago, IL 60064, USA

Distributed by:  
Abbott Laboratories, Inc.  
North Chicago, IL 60064, USA

Under license from  
Anesta Corp.  
Salt Lake City, UT 84116, USA

Top Panel

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

**Attachment 4**

***Actiq* Patient Leaflet**

**Patient Leaflet**

**Actiq®** (oral transmucosal fentanyl citrate)

58-0532

**WARNING: Keep out of the reach of children**

Read this information carefully before using Actiq. If you have any questions after reading this patient leaflet, talk to your doctor.

Actiq contains medicine that could be harmful or fatal to a child. You **MUST** keep Actiq out of the reach of children. Explain to children that Actiq is a medicine for your use only. Actiq can cause injury or death in people who are not already taking prescription opioid (narcotic) pain medicines on a regular schedule to relieve chronic cancer pain. If you have not been taking these types of medicines, do not use Actiq because it may cause your breathing to slow down to a dangerous level or even to stop. Some examples of opioid pain medicines are Duragesic®, Dilaudid®, methadone, morphine, MS Contin®, and OxyContin®.

Actiq must only be used for breakthrough cancer pain. Do not use Actiq if you have pain that will go away in a few days, such as pain from surgery, from doctor or dentist visits, or any other short-lasting pain.

Do not let anyone else use Actiq. It is for your use only.

**If someone accidentally takes Actiq:**

If the person is not awake and alert, call 911 or call for emergency help immediately.

If the person is awake and alert, call Poison Control at 1-800-690-3924.

**WARNING: MAY BE HABIT FORMING**

**WARNING: Keep out of the reach of children**

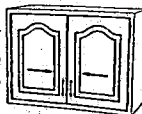
**Important Information For People Who Have Children In The Home:** You **MUST** keep Actiq out of the reach of children. Actiq contains medicine that could be harmful or fatal to a child. Please pay close attention to the child warnings in this patient leaflet.

**How to use the Actiq Welcome Kit**

You have been prescribed an Actiq Welcome Kit to help you store Actiq and your other medicines out of the reach of children. It is very important that you use the items in the Actiq Welcome Kit to protect the children in your home.

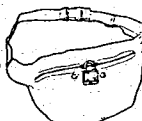
**Child-resistant lock**

After you have chosen a storage space for Actiq and your other medicines, secure this space with the child-resistant lock included in the Welcome Kit.



**Portable locking pouch**

You may keep a small supply of Actiq in the portable locking pouch so that it is nearby for your immediate use. The rest of your Actiq must be kept in the locked storage space. Keep this pouch secured with its lock and keep it out of the reach and sight of children.



**Child-resistant temporary storage bottle**

If for some reason you cannot finish the entire Actiq unit and cannot immediately dissolve the medicine under hot tap water, immediately put the Actiq in the temporary storage bottle for safe keeping. Push the Actiq unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the Actiq unit as soon as you can (see How to dispose of Actiq after use).

If you did not receive an Actiq Welcome Kit, please call 1-888-818-4113.



**How to store Actiq in your home**

- Actiq and your other medicines must be stored in a locked storage space. Be sure to use the child-resistant lock that you received in the Welcome Kit.
- Always keep Actiq in its foil package until you are ready to use it. Do not use Actiq if the foil package has been damaged or opened before you are ready to use it.
- Store Actiq at room temperature. Do not refrigerate or freeze. Do not store Actiq above 86°F (30°C). Remember, the inside of your car can get hot in the summer.

**What is Actiq?**

Actiq contains a prescription opioid (narcotic) pain-relieving medicine called fentanyl. When you place Actiq in your mouth, it slowly dissolves and the medicine is absorbed through the lining of your mouth. From your mouth, it goes into your bloodstream, where it works to relieve your breakthrough cancer pain.

**When to use Actiq**

Actiq is used to relieve the flares called breakthrough cancer pain, that your regularly prescribed pain medicine does not control. Actiq should be taken along with your regularly prescribed cancer pain medicine. Do not stop taking your regularly prescribed pain medicine.

**When not to use Actiq**

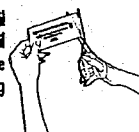
- You should **not** use Actiq if you are having short-term pain, including pain from injuries and surgery.
- You should **not** use Actiq unless you have breakthrough cancer pain and have been taking a prescription opioid (narcotic) pain medicine every day on a regular schedule.

**How to use Actiq**

When you first start using Actiq, your doctor will help you find the dose of Actiq that will relieve your pain. Use Actiq exactly as your doctor or nurse told you to use it. Your doctor will tell you how often you can take Actiq safely.



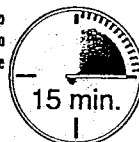
**Step 1.** Each Actiq unit is sealed in its own foil package. Do not open the package until you are ready to use Actiq. When you are ready to use Actiq, cut open the package using scissors and remove the Actiq unit.



**Step 2.** Place Actiq in your mouth between your cheeks and gums and actively suck on the medicine. Move Actiq around in your mouth, especially along your cheeks. Twirl the handle often.



Finish the Actiq completely in 15 minutes to get the most relief. If you finish Actiq too quickly, you will swallow more of the medicine and get less relief.



have an episode of breakthrough cancer pain, you should call your doctor or nurse.

**Do not bite or chew Actiq.** You will get less relief of your breakthrough cancer pain.

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

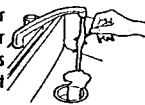
You may drink some water before using Actiq, but you should not drink or eat anything while using Actiq.

#### **How to dispose of Actiq after use**

Partially used Actiq units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed Actiq. You must immediately and properly dispose of the Actiq handle after use even if there is little or no medicine left on it. Please follow these directions to dispose of the handle:

1. Once you have finished the Actiq unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

2. If any medicine remains on the handle after you have finished, place the handle under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets.



3. If you did not finish the entire Actiq unit and you cannot immediately dissolve the medicine under hot running water, put the Actiq in the temporary storage bottle that you received in the Actiq Welcome Kit for safe keeping. Push the Actiq unit into the opening on the top until it falls completely into the bottle. Never leave unused or partly used Actiq units where children or pets can get to them.

4. Dispose of the handles in the temporary storage bottle as soon as you can by following the directions in steps 1 and 2. You must dispose of all handles in the temporary storage bottle at least once a day.

Do not flush entire unused Actiq units, Actiq handles, or foil pouches down the toilet.

#### **What to expect from Actiq**

You should begin to feel some relief while you are taking Actiq. You may not get full relief for up to 45 minutes after you have finished taking Actiq. If you do not get enough pain relief from just one Actiq, your doctor may allow you to use another one. Do not use a second Actiq unless your doctor or nurse tells you that you may do so.

Some people will have side effects with Actiq. The most common side effects are feeling sleepy, sick to your stomach, or dizzy. If you begin to feel very sleepy, remove the Actiq from your mouth or call another person in your household to help you.

For best results, let your doctor or nurse know about your pain and how Actiq is working for you so the dose can be changed, if needed.

#### **Important safety information for patients and caregivers**

You and the other people in your home should be aware of some important information about Actiq. Always feel free to contact your doctor or nurse with any questions or concerns you may have about Actiq and any side effects.

- A serious side effect of Actiq is slow, shallow breathing. This can occur if your dose of Actiq is too high or if you take too much Actiq. You and your caregivers should discuss this side effect with your doctor. **Attention Caregivers:** If you see that the person taking Actiq has slow breathing or if you have a hard time waking the person up, remove the Actiq from their mouth and call for emergency help. (See What to do if a child or an adult accidentally takes Actiq.)

- Actiq may change the effect of other medicines (prescription and over-the-counter). Actiq will also add to the effects of alcohol and medicines that make you sleepy (like sleeping pills, anxiety medicines, antihistamines, or tranquilizers). Make sure that you talk to your doctor before drinking alcohol or taking any medicines (other than your regularly scheduled opioid [narcotic] pain medicines) while using Actiq.

Discuss this with your doctor to get advice on whether it is safe for you to drive or operate machinery. Until you have experienced how this medicine affects you, do not drive a car or operate potentially dangerous machinery. You should discuss this further with your doctor.

- Do not use Actiq if you are pregnant or nursing unless told that you may do so by your doctor.

#### **What to do if a child or an adult accidentally takes Actiq**

Actiq contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed Actiq. In these people, Actiq can cause their breathing to slow down or even stop. If you think someone has accidentally taken Actiq, follow these steps immediately:

1. Remove the Actiq unit from the person's mouth.

2. If the person is asleep, keep them awake by calling their name and shaking their arm or shoulder.

3. If the person is not awake and alert, call 911 or call for emergency help. If the person is awake and alert, call Poison Control at 1-800-690-3924.

#### **While waiting for emergency help:**

4. If the person seems to be breathing slowly, every 5 to 10 seconds tell them to breathe.

5. If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.

#### **How to know if someone has accidentally taken Actiq**

If someone has accidentally taken Actiq, they may have these symptoms:

- Very sleepy
- Itching, especially around the nose and eyes
- Dizzy
- Sick to their stomach or vomiting
- Not breathing or breathing very slowly

#### **When to call your doctor or nurse**

- If you have side effects that bother you and do not go away.
- If you want to take any over-the-counter medicines.
- If another doctor has prescribed any new medicines for you.
- If you do not get enough breakthrough cancer pain relief.
- If you are using Actiq more than four times a day.
- If you are not finishing the entire Actiq unit.

#### **When Actiq is no longer needed**

If you are no longer using Actiq or if you have unused Actiq in your home, please follow these steps to dispose of the Actiq as soon as possible:

Step 1. Remove all Actiq from the locked storage space.

Step 2. Remove one Actiq unit from its pouch using scissors, and hold the Actiq by its handle over the toilet bowl.

Step 3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.

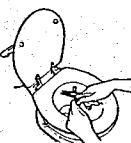
Step 4. Throw the handle away in a place that is out of the reach of children.

Step 5. Repeat steps 2, 3, and 4 for each Actiq.

Flush the toilet twice after 5 Actiq units have been cut. Do not flush more than 5 Actiq units at a time.

Do not flush entire unused Actiq units, Actiq handles, or foil pouches down the toilet.

If you need help with disposal of Actiq, call 1-800-615-0187. If you still need help, call your local Drug Enforcement Administration (DEA) office.



**WARNING: Keep out of the reach of children**

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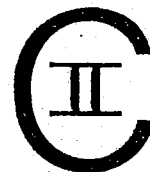
**Attachment 5**

***Actiq* Package Insert**

Tear to open



**Actiq<sup>®</sup>**  
(oral transmucosal  
fentanyl citrate)



**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 non-tolerant 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 open units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

**WARNING: May be habit forming**

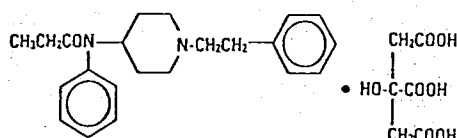
58-0551-R1-Rev. Nov., 1998

### DESCRIPTION

*Actiq* (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

*Actiq* is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

**Active Ingredient:** Fentanyl citrate, USP is *N*-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



*Actiq* is available in six strengths equivalent to 200, 400, 600, 800, 1200, or 1600 mcg fentanyl base that is identified by the text on the foil pouch, the shelf carton, and the dosage unit handle.

**Inactive Ingredients:** Sucrose, liquid glucose, artificial raspberry flavor, and white dispersion G.B. dye.

### CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

#### Pharmacology:

Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid mu-receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacologic effects of the interaction of fentanyl with mu-receptors are analgesia and sedation.

Other opioid effects may include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria and confusion or difficulty in concentrating at clinically relevant doses.

#### Clinical Pharmacology

##### Analgesia:

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see

#### **DOSAGE AND ADMINISTRATION).**

##### **Gastrointestinal (GI) Tract and Other Smooth Muscle:**

Opioids increase the tone and decrease contractions of the smooth muscle of the gastrointestinal (GI) tract. This results in prolongation in GI transit time and may be responsible for the constipating effect of opioids. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others, difficulty in urination.

##### **Respiratory System:**

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC<sup>®</sup>) administration and may persist for several hours.

Serious or fatal respiratory depression can occur, even at recommended doses, in vulnerable individuals. As with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals.

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

**(See BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.)**

##### **Pharmacokinetics**



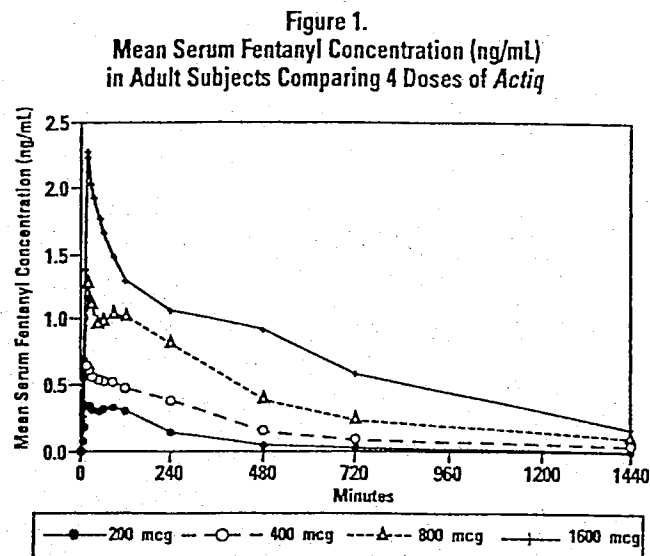
#### Absorption:

The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

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

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 dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

Dose proportionality among four 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 four doses of *Actiq* are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose 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 *Actiq* administered.



The pharmacokinetic parameters of the four strengths of *Actiq* tested in the dose-proportionality study are shown in Table 1. The mean  $C_{max}$  ranged from 0.39 - 2.51 ng/mL. The median time of maximum plasma concentration ( $T_{max}$ ) across these four doses of *Actiq* varied from 20 - 40 minutes (range of 20-480 minutes) after a standardized consumption time of 15 minutes.

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

Pharmacokinetic Parameter	200 mcg	400 mcg	800 mcg	1600 mcg
T <sub>max</sub> , minute median (range)	40 (20-120)	25 (20-240)	25 (20-120)	20 (20-480)
C <sub>max</sub> , ng/mL mean (% CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC <sub>0-140</sub> , ng/mL minute mean (% CV)	102 (65)	243 (67)	573 (64)	1026 (67)
t <sub>1/2</sub> , minute mean (% CV)	193 (48)	386 (115)	381 (55)	358 (45)

**Distribution:**

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V<sub>SS</sub>) was 4 L/kg.

**Metabolism:**

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies (see **PRECAUTIONS: Drug Interactions** for additional information).

**Elimination:**

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg). The terminal elimination half-life after *OTFC* administration is about 7 hours.

**Special Populations:**

Elderly Patients:

Elderly patients have been shown to be twice as sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. While a formal study evaluating the safety profile of *Actiq* in the elderly population has not been performed, in the 257 opioid tolerant cancer patients studied with *Actiq*, approximately 20% were over age 65 years. No difference was noted in the safety profile in this group compared to those aged less than 65 years, though they did titrate to lower doses than younger patients (see **PRECAUTIONS**).

Patients with Renal or Hepatic Impairment:

*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 **PRECAUTIONS**).

Although fentanyl kinetics are known to be altered in both hepatic and renal disease due to alterations in metabolic clearance and plasma proteins, individualized doses of *Actiq* have been used successfully for breakthrough cancer pain in patients with hepatic and renal disorders. The duration of effect for the initial dose of fentanyl is determined by redistribution of the drug, such that diminished metabolic clearance may only become significant with repeated dosing or with excessively large single doses. For these reasons, while doses titrated to clinical effect are recommended for all patients, special care should be taken in patients with severe hepatic or renal disease.

#### Gender

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse events.

#### **CLINICAL TRIALS**

##### **Breakthrough Cancer Pain:**

*Actiq* was investigated in clinical trials involving 257 opioid tolerant adult cancer patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in cancer patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of *Actiq* to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200 and 1600 mcg). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of *Actiq* could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

The successful dose of *Actiq* for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and is thus best determined by dose titration.

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of *Actiq* for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 2.

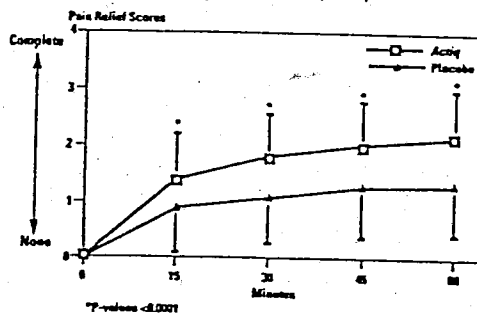
**Table 2.**  
**Successful Dose of Actiq**  
**Following Initial Titration**

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

On average, patients over 65 years of age titrated to a mean dose that was about 200 mcg less than the mean dose to which younger adult patients were titrated.

*Actiq* produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration (see Figure 2).

**Figure 2**  
**Pain Relief (PR) Scores (Mean $\pm$ SD) During the Double-Blind Phase-All Patients with Evaluable Episodes on Both *Actiq* and Placebo (N=86)**



In this same study patients also rated the performance of medication to treat their breakthrough cancer pain using a different scale ranging from "poor" to "excellent." On average, placebo was rated "fair" and *Actiq* was rated "good."

#### **INDICATIONS AND USAGE**

(See BOX WARNING and CONTRAINDICATIONS)

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

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

*Actiq* should be individually titrated to a dose that provides adequate analgesia and minimizes side effects. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased (see DOSAGE AND ADMINISTRATION).

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount that 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 in a secured container.

#### **CONTRAINDICATIONS**

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 risk of respiratory depression begins to increase with fentanyl plasma levels of 2.0 ng/mL in opioid non-tolerant individuals (see Pharmacokinetics). This product must not be used in opioid non-tolerant 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.

*Actiq* is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

#### **WARNINGS**

##### **See BOX WARNING**

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 (e.g., erythromycin, ketoconazole, and certain protease inhibitors), and alcoholic beverages may produce increased depressant effects. Hypoventilation, hypotension, and profound sedation may occur.

*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.

**Pediatric Use:** The appropriate dosing and safety of *Actiq* in opioid tolerant children with breakthrough cancer pain have not been established below the age of 16 years.

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 both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See SAFETY AND HANDLING, PRECAUTIONS, and PATIENT LEAFLET for specific patient instructions.)

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home on a full time or visiting basis and counsel them regarding the dangers to children from inadvertent exposure.

## **PRECAUTIONS**

### **General**

The initial dose of *Actiq* to treat episodes of breakthrough cancer pain should be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., 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. (See **WARNINGS**.)

### **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.

### **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<sub>2</sub> 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.

### **Cardiac Disease**

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

### **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**).

### **Information for Patients and Their Caregivers**

Patients and their caregivers must be instructed that *Actiq* contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible. (See **SAFETY AND HANDLING, WARNINGS, and PATIENT LEAFLET** for specific patient instructions.)

Patients and their caregivers should be provided with an *Actiq* Welcome Kit, which contains educational materials and safe storage containers to help patients store *Actiq* and other medicines out of the reach of children. Patients and their caregivers should also have an opportunity to watch the patient safety video, which provides proper product use, storage, handling and disposal directions. Patients should also have an opportunity to discuss the video with their health care providers. Health care professionals should call 1-888-818-4113 to obtain a supply of welcome kits or videos for patient viewing.

### **Disposal of Used *Actiq* Units**

Patients must be instructed to dispose of completely used and partially used *Actiq* units.

- 1) After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
- 2) If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
- 3) Handles in the child-resistant container should be disposed of (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the *Actiq* unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

**Disposal of Unopened *Actiq* Units When No Longer Needed**

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused *Actiq* units:

- 1) Remove the *Actiq* unit from its pouch using scissors, and hold the *Actiq* by its handle over the toilet bowl.
- 2) Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
- 3) Dispose of the handle in a place that is out of the reach of children.
- 4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire *Actiq* units, *Actiq* handles, foil pouches, or cartons down the toilet. The handle should be disposed of where children cannot reach it (see **SAFETY AND HANDLING**).

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of *Actiq* are provided in the *Actiq* Patient Leaflet. Patients should be encouraged to read this information in its entirety and be given an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, they should be instructed to call the toll-free number (1-800-615-0187) or seek assistance from their local DEA office.

**Laboratory Tests**

The effects of *Actiq* on laboratory tests have not been evaluated.

**Drug Interactions**

See **WARNINGS**.

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*. Thus patients who begin or end therapy with potent inhibitors of CYP450 3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole and itraconazole), and protease inhibitors (e.g., ritonavir) while receiving *Actiq* should be monitored for a change in opioid effects and, if warranted, the dose of *Actiq* should be adjusted.

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

Because animal carcinogenicity studies have not been conducted with fentanyl citrate, the potential carcinogenic effect of *Actiq* is unknown.

Standard mutagenicity testing of fentanyl citrate has been conducted. There was no evidence of mutagenicity in the Ames *Salmonella* or *Escherichia* mutagenicity assay, the *in-vitro* mouse lymphoma mutagenesis assay, and the *in-vivo* micronucleus cytogenetic assay in the mouse.

Reproduction studies in rats revealed a significant decrease in the pregnancy rate of all experimental groups. This decrease was most pronounced in the high dose group (1.25 mg/kg subcutaneously) in which one of twenty animals became pregnant.

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

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

No evidence of teratogenic effects has been observed after administration of fentanyl citrate to rats. There are no adequate and well-controlled studies in pregnant women. *Actiq* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **Labor and Delivery**

*Actiq* is not indicated for use in labor and delivery.

#### **Nursing Mothers**

Fentanyl is excreted in human milk; therefore *Actiq* should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants.

#### **Pediatric Use**

See **WARNINGS**.

#### **Geriatric Use**

Of the 257 patients in clinical studies of *Actiq* in breakthrough cancer pain, 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.

#### **ADVERSE REACTIONS**

##### **Pre-Marketing Clinical Trial Experience**

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 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.

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.

Because the clinical trials of *Actiq* were designed to evaluate safety and efficacy in treating breakthrough cancer pain, 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 breakthrough cancer pain 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 breakthrough cancer pain. 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. Table 3 lists by dose groups, adverse events with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. 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.



**Table 3.**  
**Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of**  
**Particular Clinical Interest Which Occurred During Titration (Events in 1% or More of Patients)**

Body Group	200 800 mcg	800- 1400 mcg	1400 mcg	>1400 mcg	Any
Number of Patients	238	138	54	41	254
Body As A Whole					
Asthenia	8	4	8	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	8	2
Digestive					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	8	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	9	3	11	20	17
Confusion	1	6	2	8	4
Anxiety	2	8	2	9	3
Abnormal Gait	8	1	4	8	2
Dry Mouth	1	1	2	8	2
Nervousness	1	1	0	8	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Incontinence	0	1	2	8	1
Thinking	0	1	2	0	1
Abnormal					
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	8	5	2
Itch	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	8	2	8	2

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

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

**Cardiovascular:** Migraine

**Digestive:** Diarrhea, dyspepsia, flatulence

**Metabolic and Nutritional:** Peripheral edema, dehydration

**Nervous:** Hypesthesia

**Respiratory:** Pharyngitis, cough increased

The following events occurred during titration with an overall frequency of less than 1% and are listed in descending order of frequency within each body system.

**Body as a Whole:** Flu syndrome, abscess, bone pain

**Cardiovascular:** Deep thrombophlebitis, hypertension, hypotension

**Digestive:** Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

**Hemic and Lymphatic:** Anemia, leukopenia

**Metabolic and Nutritional:** Edema, hypercalcemia, weight loss

**Musculoskeletal:** Myalgia, pathological fracture, myasthenia

**Nervous:** Abnormal dreams, urinary retention, agitation, amnesia, emotional lability, euphoria, incoordination, libido decreased, neuropathy, paresthesia, speech disorder

**Respiratory:** Hemoptysis, pleural effusion, rhinitis, asthma, hiccup, pneumonia, respiratory insufficiency, sputum increased

**Skin and Appendages:** Alopecia, exfoliative dermatitis

**Special Senses:** Taste perversion

**Urogenital:** Vaginal hemorrhage, dysuria, hematuria, urinary incontinence, urinary tract infection

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 4 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.

Table 4  
Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment (Events in 1% or More of Patients)

Dose Group	200- 800 mcg	800- 1400 mcg	1600 mcg	>1600 mcg	Any
Number of Patients	36	33	53	27	152
Body As A Whole					
Asthenia	25	30	17	25	36
Headache	12	17	13	4	28
Accidental Injury	4	6	4	7	5
Hypertonia	2	2	2	8	3
Digestive					
Nausea	31	36	25	28	65
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	28
Intestinal Obstruction	0	2	4	8	3
Cardiovascular					
Hypotension	1	1	8	8	1
Nerves					
Dizziness	12	18	9	8	16
Anxiety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confusion	2	5	8	7	15
Depression	9	4	13	7	16
Insomnia	5	1	2	7	9
Abnormal Gait	5	1	8	4	7
Dry Mouth	3	1	8	8	4
Nervousness	3	1	2	4	4
Sleep	2	2	6	4	3
Vasodilatation	4	1	8	8	3
Thinking Abnormal	2	1	8	8	2
Abnormal Dreams	1	1	8	8	1
Convulsion	0	1	2	8	1
Myoclonus	0	0	4	8	1
Tremor	0	1	2	8	1
Vertigo	0	8	4	8	1
Respiratory					
Dyspnea	15	16	8	7	22
Skin					
Rash	3	5	8	4	8
Sweating	3	2	2	8	4
Pruritus	2	0	2	8	2
Special Senses					
Abnormal Vision	2	2	8	8	3
Urinary					
Retention	1	2	8	8	2

The following events not reflected in Table 4 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

**Body as a Whole:** Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

**Cardiovascular:** Deep thrombophlebitis, migraine, palpitation, vascular disorder

**Digestive:** Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

**Hemic and Lymphatic:** Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

**Metabolic and Nutritional:** Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

**Musculoskeletal:** Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

**Nervous:** Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

**Respiratory:** Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

**Skin and Appendages:** Skin ulcer, alopecia

**Special Senses:** Tinnitus, conjunctivitis, ear disorder, taste perversion

**Urogenital:** Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

The following events occurred with a frequency of less than 1% in the long-term extension study and are listed in descending order of frequency within each body system.

**Body as a Whole:** Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

**Cardiovascular:** Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

**Digestive:** Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

**Hemic and Lymphatic:** Bleeding time increased

**Metabolic and Nutritional:** Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

**Musculoskeletal:** Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

**Nervous:** Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

**Respiratory:** Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

**Skin and Appendages:** Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

**Special Senses:** Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness

**Urogenital:** Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

#### **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

#### **OVERDOSAGE**

##### **Clinical Presentation**

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

##### **General**

Immediate management of opioid overdose includes removal of the *Actiq* unit, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

##### **Treatment of Overdose (Accidental Ingestion) in the Opioid NON-Tolerant Person**

Ventilatory support should be provided, intravenous access obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

##### **Treatment of Overdose in Opioid-Tolerant Patients**

Ventilatory support should be provided and intravenous access obtained as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

##### **General Considerations for Overdose**

Management of severe *Actiq* overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of *Actiq*, this is possible with fentanyl and other opioids. If it occurs, it should be managed by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

#### **DOSAGE AND ADMINISTRATION**

**Actiq is contraindicated in non-opioid tolerant individuals.**

*Actiq* should be individually titrated to a dose that provides adequate analgesia and minimizes side effects (see Dose Titration).

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

Physicians and dispensing pharmacists must specifically question patients and caregivers about the presence of children in the home on a full time or visiting basis and counsel accordingly regarding the dangers to children of inadvertent exposure to *Actiq*.

#### **Administration of Actiq**

The foil 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 one 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.

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 (see Disposal Instructions).

#### **Dose Titration**

**Starting Dose:** The initial dose of *Actiq* to treat episodes of breakthrough cancer pain should be 200 mcg. Patients should be prescribed an initial titration supply of six 200 mcg *Actiq* units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose.

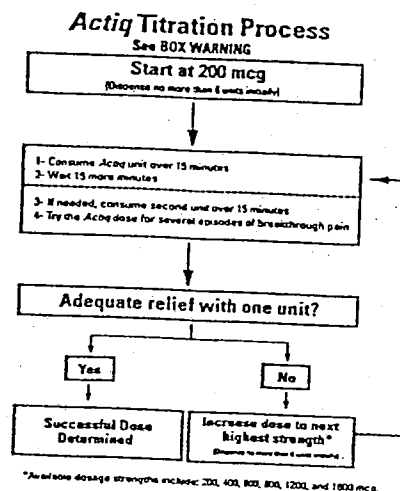
From this initial dose, patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single *Actiq* dosage unit per breakthrough cancer pain episode.

Patients should record their use of *Actiq* over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

**Redosing Within a Single Episode:** Until the appropriate dose is reached, patients may find it necessary to use an additional *Actiq* unit during a single episode. Redosing may start 15 minutes after the previous unit has been completed (30 minutes after the start of the previous unit). While patients are in the titration phase and consuming units which individually may be subtherapeutic, no more than two units should be taken for each individual breakthrough cancer pain episode.

**Increasing the Dose:** If treatment of several consecutive breakthrough cancer pain episodes requires more than one *Actiq* per episode, an increase in dose to the next higher available strength should be considered. At each new dose of *Actiq* during titration, it is recommended that six units of the titration dose be prescribed. Each new dose of *Actiq* used in the titration period should be evaluated over several episodes of breakthrough cancer pain (generally 1-2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

**Daily Limit:** Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day. If consumption increases above four units/day, the dose of the long-acting opioid used for persistent cancer pain should be re-evaluated.



#### Dosage Adjustment

Experience in a long-term study of *Actiq* used in the treatment of breakthrough cancer pain suggests that dosage adjustment of both *Actiq* and the maintenance (around-the-clock) opioid analgesic may be required in some patients to continue to provide adequate relief of breakthrough cancer pain.

Generally, the *Actiq* dose should be increased when patients require more than one dosage unit per breakthrough cancer pain episode for several consecutive episodes. When titrating to an appropriate dose, small quantities (six units) should be prescribed at each titration step. Physicians should consider increasing the around-the-clock opioid dose used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

#### Discontinuation of Actiq

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

#### SAFETY AND HANDLING

*Actiq* is supplied in individually sealed child-resistant foil pouches. The amount of fentanyl contained in *Actiq* can be fatal to a child. Patients and their caregivers must be instructed to keep *Actiq* out of the reach of children (see BOX WARNING, WARNINGS, PRECAUTIONS and PATIENT LEAFLET).

Store at 25°C (77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

*Actiq* should be protected from freezing and moisture. Do not store above 25°C. Do not use if the foil pouch has been opened.

#### **DISPOSAL OF ACTIQ**

Patients must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. 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 pouch, yet may contain enough medicine to be fatal to a child (see Information for Patients).

A temporary storage bottle is provided as part of the Actiq Welcome Kit (see Information for Patients and Their Caregivers). This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the patient leaflet.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in Information for Patients and Their Caregivers and in the patient leaflet. If additional assistance is required, referral to the Actiq 800# (1-800-615-0187) should be made.

#### **HOW SUPPLIED**

Actiq is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective foil pouch. These foil pouches are packed 24 per shelf carton for use when patients have been titrated to the appropriate dose.

Patients should be prescribed an initial titration supply of six 200 mcg Actiq units. At each new dose of Actiq during titration, it is recommended that only six units of the next higher dose be prescribed.

Each dosage unit has a white to off-white color. The dosage strength of each unit is marked on the handle, the foil pouch and the carton. See foil pouch and carton for product information.

Dosage Strength (fentanyl base)	Carton/Foil Pouch Color	NDC Number
200 mcg	Gray	NDC 0074-2460-24
400 mcg	Blue	NDC 0074-2461-24
600 mcg	Orange	NDC 0074-2462-24
800 mcg	Purple	NDC 0074-2463-24
1200 mcg	Green	NDC 0074-2464-24
1600 mcg	Burgundy	NDC 0074-2465-24

Note: Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Rx only.

DEA order form required. A Schedule CII narcotic.

Manufactured by ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA  
Distributed by ABBOTT LABORATORIES, INC., NORTH CHICAGO, IL 60064, USA

Under license from ANESTA CORP., Salt Lake City, UT 84116, USA  
U. S. Patent No. 4,671,953  
Printed in USA

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Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

## **Attachment 6**

### **Elements of RMP to be included in Speaker Bureau Training**



## Elements of Risk Management Program to be Included in Speaker Bureau Training

- Program Objectives -- to address three key potential risk situations
- Professional Product Labeling -- with particular attention paid to the boxed warnings
  - Indication
  - Prescribing Directions -- importance of small counts during titration and of completing units
- Patient Leaflet
  - Child safety messages (including proper storage and disposal)
  - Emergency information, including 1-800 # for accidental ingestion
  - Patient selection information
- Product presentation
  - Product Definition
  - Packaging (pouch and shelf carton) -- *warnings*
- Welcome Kit -- purpose and contents, with emphasis on
  - In-home secure containers (child safety lock, secure personal container)
  - Temporary storage container
  - Children's booklet
  - Patient Leaflet
- Safety Video
- How to contact Abbott/Anesta for additional information
  - 1-800#
  - Website
  - CD-ROM program access

**Attachment 7**

***Actiq* CD-ROM Schematic**

Abbott HPD  
ACTIQ CD-ROM--Module For Nurses  
G & A Job #: AB 6313  
Abbott Project #: 96-526C  
October 29, 1997  
Version 1.0

SCREEN # **1**

**Main Title screen**

Prehead:

From Abbott Laboratories and the Anesta Corporation

Graphic:

[4-color photo image of the iceberg breaking through the water]

Headline:

Using

Logo:

ACTIQ™

(oral transmucosal fentanyl citrate) CR

For the Management of Breakthrough Pain

Subhead:

A dosing and administration guide for health care professionals  
involved with treating cancer pain

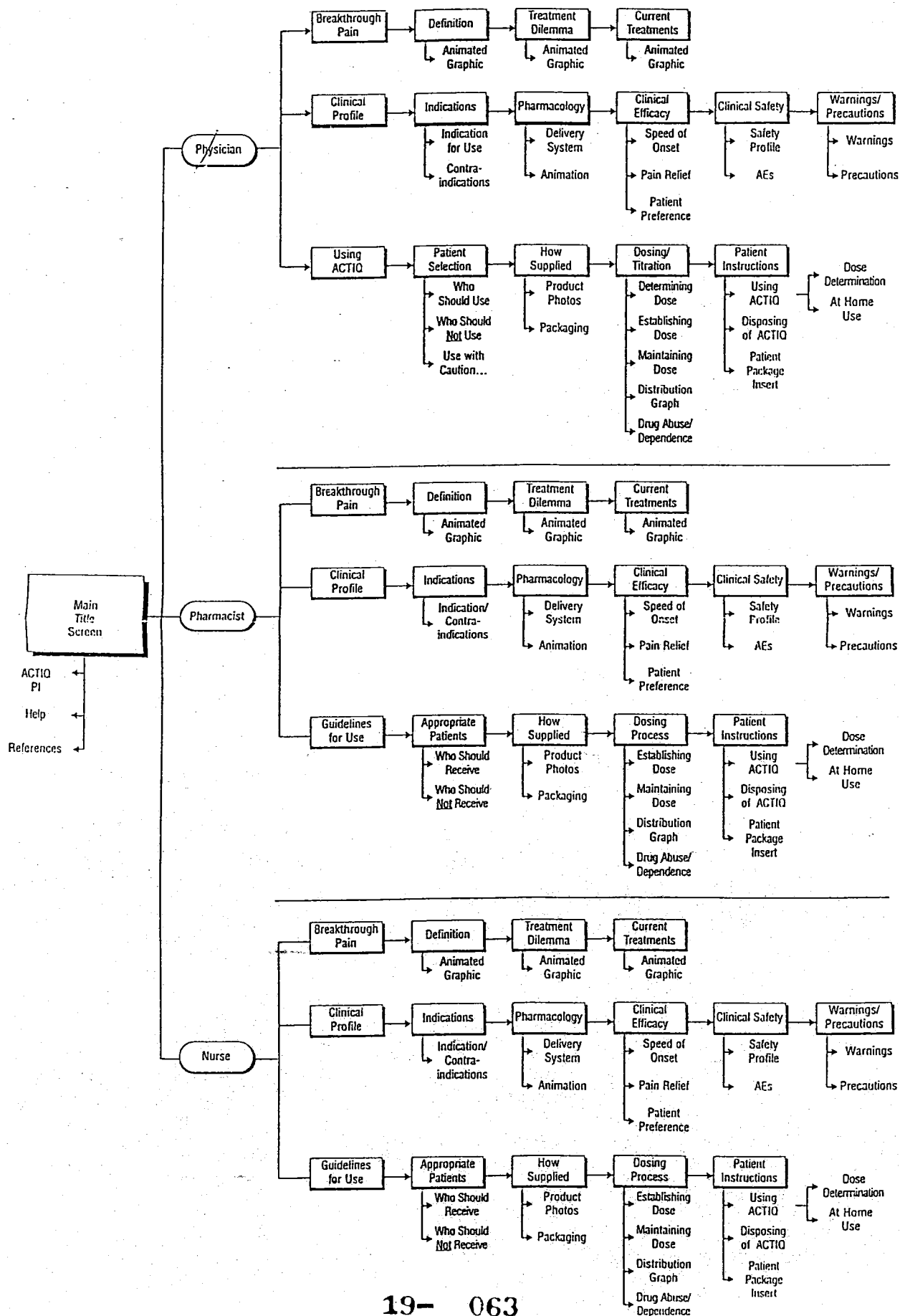
Menu buttons:

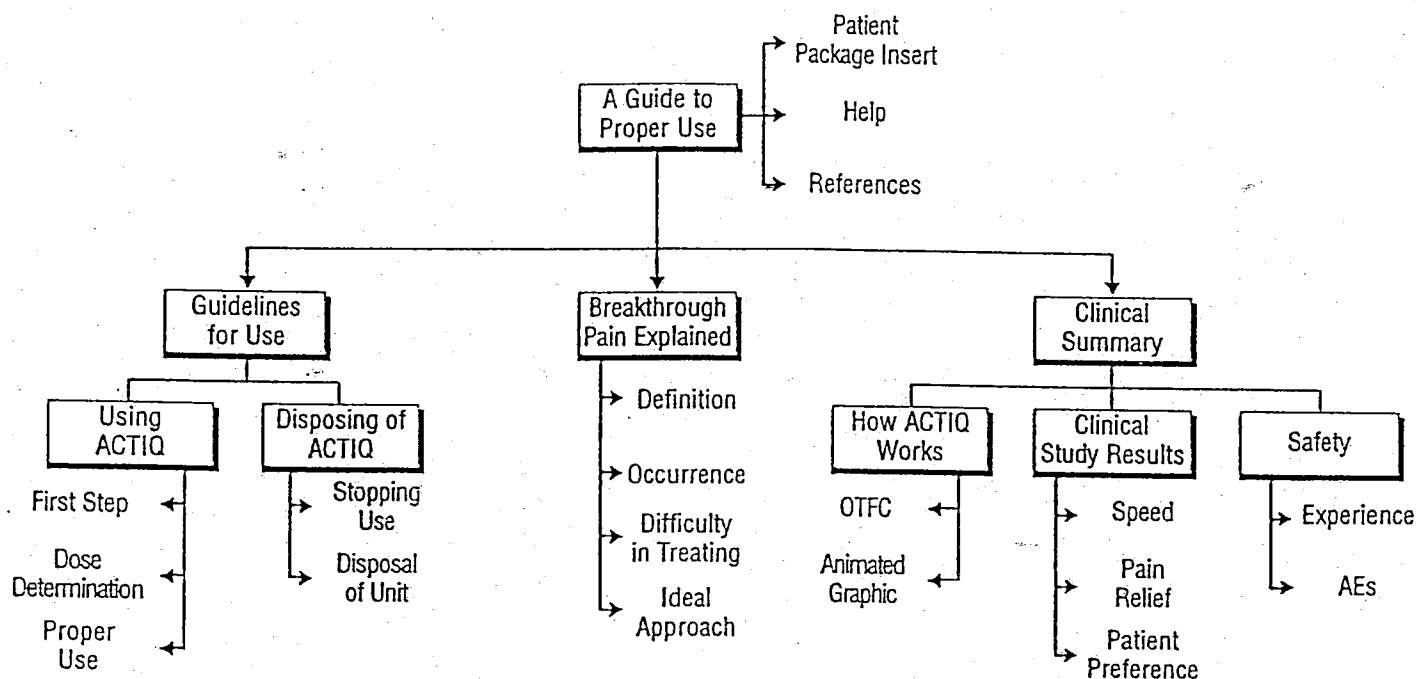
Please indicate your professional status \*

**Physician**

**Pharmacist**

**Nurse**





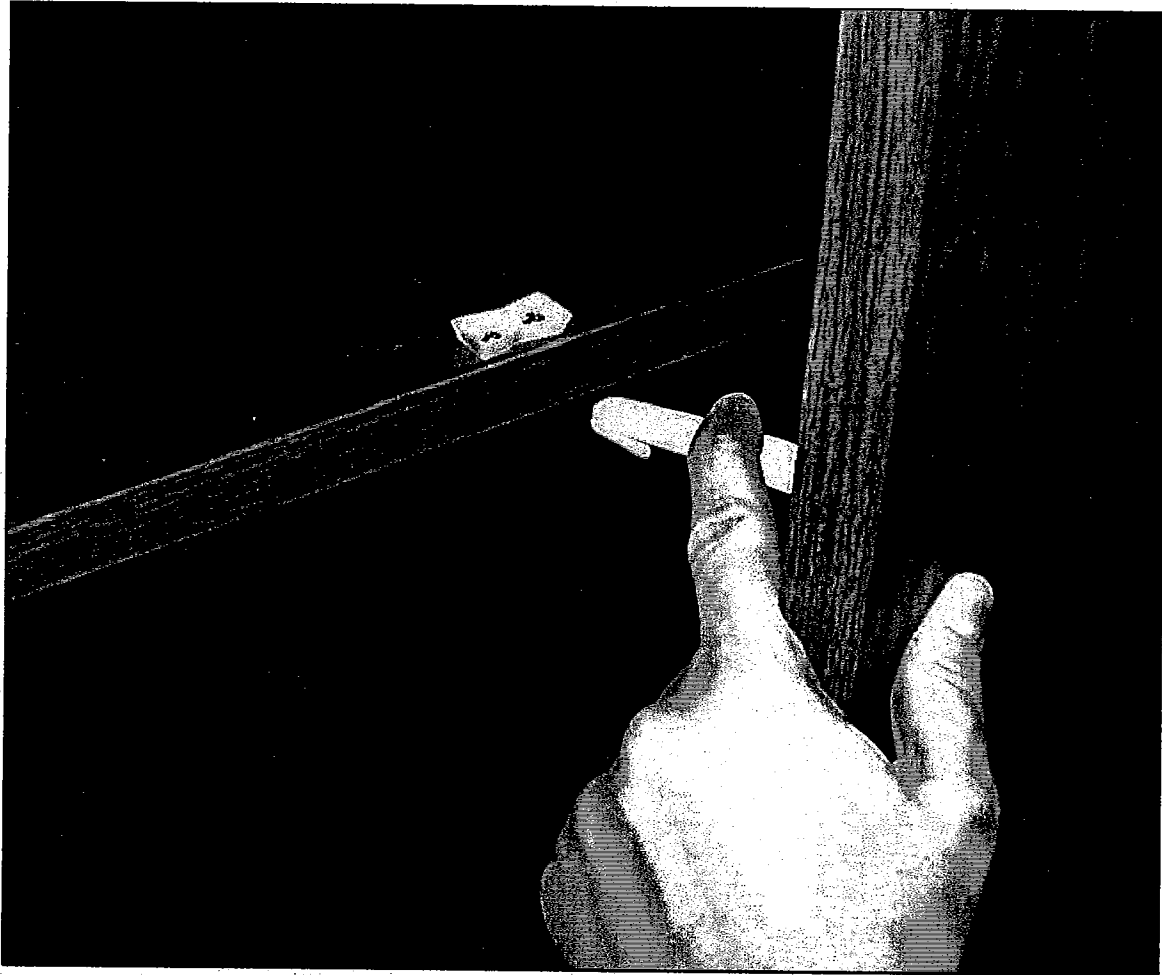
## **Attachment 8**

### **Child Safety Lock**

# Child Safety Lock



## Child Safety Lock Installed in Cabinet





## **Attachment 9**

### **Secure Personal Container (ie “fanny pack”)**

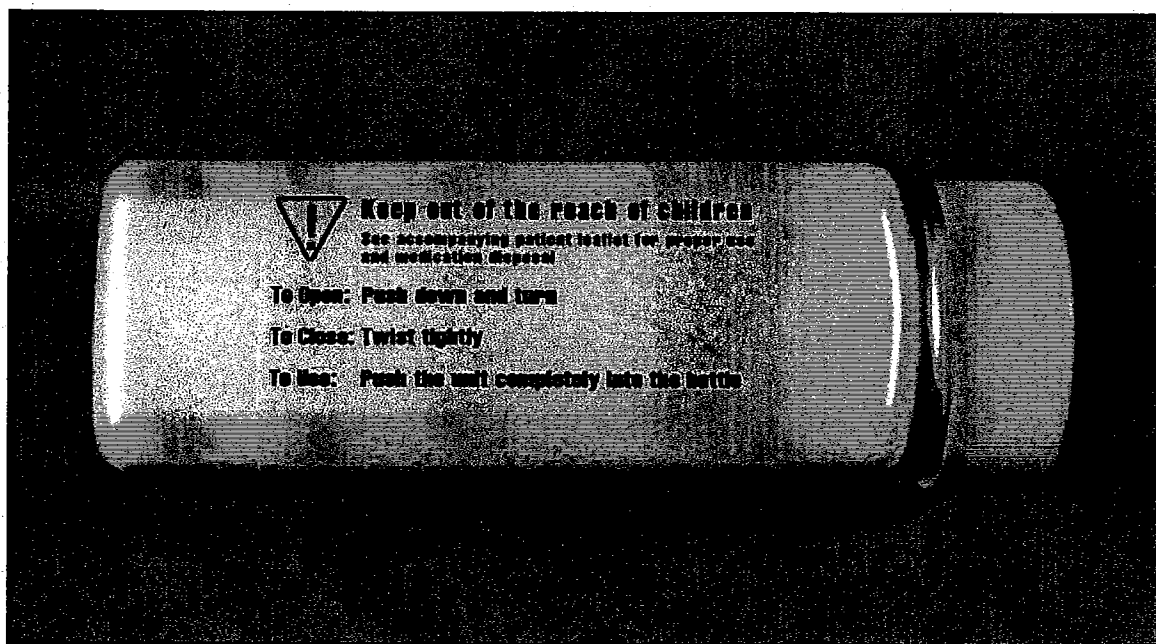
Secure Personal Container (ie, "fanny pack")



## **Attachment 10**

### **Child-resistant Temporary Storage Container**

## Child-resistant Temporary Storage Container



**Attachment 11**

**Pharmacy Computer Warning screens**

Patient Screen

1 003360 Name: Patient XYZ ANY Prod: Actiq 200mcg Home: RXD Sex: M  
 2 Addr: 1234 Any St. Anytown, USA Zip: 00000 Tel: www-xxx-yyy  
 3 Allergies: NKA S.C.  
 4 Comment: NONE PT: Disc: 00%  
 5 Type: MC Pln: Grp: Id: 123456789A Copay: .00  
 6 C/H: Patient F/N: ANY ELIG: I SPCV: L#: ExDt:  
 Treatment Change Mode

TYP	CAT	TEXT
1	0	0
2	0	0 Has young children in the home!!!!!!!
3	0	0
4	0	0 Is also taking ATC opioids

Prescription Filling Screen

Enter CMT, E, D1-D10, I1-I10, C1-C10, <APC>, <DPC>, <ESC>: .

1 003360 Name: Patient XYZ ANY Prod: Actiq 200mcg Home: RXD Sex: M  
 2 Addr: 1234 Any St. Anytown, USA Zip: 00000 Tel: www-xxx-yyy  
 3 Allergies: NKA S.C.  
 4 Comment: NONE PT: Disc: 00%  
 5 Type: MC Pln: Grp: Id: 123456789A Copay: .00  
 6 C/H: Patient F/N: ANY ELIG: I SPCV: L#: ExDt:  
 Lst AWP Upd 1-14-98  
 7 Rx#: 0000000 Drug: Actiq 200mcg 11111-1111-11 Cost: .00  
 8 QtyW: 24 Strength: 200mcg Form: P.O. QtyD: 1 Date: xx-yy-zz  
 9 # Days: 5 Refill: 0 Doctor: AEMC DEA#: AE2409046 OT00250  
 10 Bill: Rlt: Price: \$ xxx Copay: xx Rph: BM Tech: DAW  
 11 Instr: USE AS DIRECTED FOR BREAKTHROUGH PAIN  
 XBX: DG:

Caution Messages

001 May Cause Drowsiness  
 002 \*\*\*\*\*ONLY FOR OPIOID TOLERANT PATIENTS \*\*\*\*\*  
 003 \*\*\*\*\*SCREEN FOR YOUNG CHILDREN IN/VISITING THE HOME\*\*\*\*\*  
 004 \*\*\*\*\*ALWAYS KEEP OUT REACH OF CHILDREN\*\*\*\*\*  
 005 \*\*\*\*\*READ ALL ENCLOSED MATERIALS CAREFULLY BEFORE USE\*\*\*\*\*

**ECKERD**

# RX ADVISOR

JANE E. CARNEY

Drug: ACTIQ 200 mcg, #24

Rx#: 6300671

Date: 1/12/98

Your Eckerd Phone#: (770) 972-8255

Directions:

DO NOT TAKE THIS MEDICINE IF YOU ARE NOT CURRENTLY TAKING OTHER STRONG PRESCRIPTION PAIN MEDICINES ON A REGULAR SCHEDULE, such as MS Contin®, Duragesic®, Oxycontin®, Percocet®, Dilaudid®, MSIR®, or Roxanol®. IF YOU ARE UNSURE ABOUT WHETHER YOU SHOULD BE TAKING ACTIQ®, CONTACT YOUR DOCTOR OR ECKERD PHARMACIST.

*Directions: Dissolve 1 unit in mouth over 15 minutes for breakthrough pain episodes. If pain persists, follow physician's instructions. Do not bite or chew unit.*

**COMMON USES:** This medicine is an potent opioid medication for controlling your breakthrough pain.

**HOW TO USE THIS MEDICINE:** Follow the directions for using this medicine provided by your doctor. THIS MEDICINE COMES WITH A PATIENT INFORMATION LEAFLET. READ IT CAREFULLY. Ask your doctor, nurse, or pharmacist any questions that you may have about this medicine. TAKE THIS MEDICINE over 15 minutes by moving it around the inside lining of your mouth. STORE THIS MEDICINE at room temperature, away from heat and ALWAYS KEEP OUT OF REACH OF CHILDREN.

**CAUTIONS:** This medication is FOR YOUR USE ONLY. NEVER LET ANYONE ELSE USE IT. Actiq® should only be used if you are already taking a strong prescription pain medicine regularly. It should not be used if you have pain that will go away in a few days or less. Actiq must be kept away from children. It contains a strong medicine that could be life threatening to a child. Never leave an unused or partially used unit out where a child or pet might reach it. Make sure you inform your doctor about any new medicines you plan to take, such as over the counter pain medications. Actiq® will add to the effects of alcohol and other depressants such as sleeping pills. Call your doctor if you require Actiq® more than 4 times a day.

**POSSIBLE SIDE EFFECTS:** COMMON SIDE EFFECTS, that may go away during treatment, include nausea, drowsiness, constipation or dizziness. The side effects from Actiq® are usually similar to those from your current pain medications. A rare but serious side effect of Actiq® is slow, shallow breathing or problems breathing. IF YOU EXPERIENCE ANY BREATHING PROBLEMS WHILE TAKING ACTIQ®, CHECK WITH YOUR DOCTOR IMMEDIATELY. If you notice other effects not listed above, contact your doctor, nurse, or pharmacist. CALL YOUR DOCTOR OR NURSE IF YOU HAVE any breathing problems, side effects that bother you or won't go away, a different doctor prescribes a new medicine for you, you are using Actiq® more than 4 times a day.

Copyright 1997 Med-Span, Inc. All rights reserved. Expires 01/1998

The information in this monograph is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects. This information is generalized and is not intended as specific medical advice. If you have questions about the drugs you are taking, check with your physician, pharmacist or nurse.

## **Attachment 12**

### **IMS National Disease and Therapeutic Index example page**





12 MONTHS					APPEARANCES (COO)				
CURRENT PRICE CURR QTR					CURRENT PRICE ALL CURR QTR				
NO	1	2	3	4	NO	1	2	3	4
CONCOMITANT DRUGS					INJECT				
USED ALONE	254	40	33	23	150	100	100	100	100
USED WITH	255	57	42	72	153	30	23	43	21
					152	70	77	51	75
MORPH/OP, N/INJ.					VISIT STAGE				
COCAINE/COCAINE, N/INJ.					FIRST				
CA/TAMSP, CYTO DTH					SUBSEQUENT				
ANTINASTHETICS					533	100	100	100	100
MIN. TRAQ. BENZODIAZ					35	5	3	23	2
CONT. PLAIN, ORAL					553	94	92	97	53
ANTILITHOTIC, SYST.					ISSUANCE				
	70	3	2	2	535	100	100	100	100
MORPHINE SULFATE					370	35	54	53	55
MORPHOL					-	-	0	5	-
PERCOCET					-	-	-	3	-
DILAUDID					-	-	-	8	-
FLAVIL					-	-	-	1	-
VALIUM					-	-	-	1	-
BACLOFEN					-	-	-	1	-
MECLIZ					-	-	-	1	-
COMPAZINE					5	3	2	6	1
MAFROSTIN					124	27	22	11	20
SENOXON S					55	12	11	15	12
AVERAGE NUMBER OF CONCOMITANT DRUGS = 0.82					REASON				
APPEARANCES (COO)					12 MONTHS				
CURRENT PRICE CURR QTR					CURRENT PRICE CURR QTR				
NO	1	2	3	4	NO	1	2	3	4
FORM					DESIRE ACTIONS				
ORAL SOLID	535	100	100	100	543	100	100	100	100
ORAL LIQUID	632	39	100	100	541	35	100	97	97
OPHTHALMIC	-	-	-	-	405	71	73	73	73
OTIC	-	-	-	-	140	25	24	15	15
NASAL	-	-	-	-	1	1	-	-	-
INJECTABLE	-	-	-	-	1	0	-	-	-
TOPICAL	-	-	-	-	-	-	-	-	-
RECTAL, SYST	-	-	-	-	NO REASON GIVEN				
INHALANTS	-	-	-	-	33	-	-	-	-
TRANSDERMAL	-	-	-	-					
ALL OTHERS	4	1	-	-					
APPEARANCES (COO)					STRENGTH				
CURRENT PRICE CURR QTR					CURRENT PRICE CURR QTR				
NO	1	2	3	4	NO	1	2	3	4
PRODUCT STRENGTH BY SIGMA					CURRENT 12 MONTHS				
CURRENT 12 MONTHS					CURRENT 12 MONTHS				

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**20-747/S003**

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

NDA 20-747/S-003

Anesta Corporation  
4745 Wiley Post Way, Suite 650  
Salt Lake City, Utah 84116

Attention: Patricia J. Richards  
Director, Regulatory Affairs

45-1  
MAR 26 1999

Dear Mrs. Richards:

We acknowledge receipt of supplemental New Drug Application (sNDA) for the following:

Name of Drug Product: Actiq (Oral transmucosal fentanyl citrate) 200 µg, 400 µg, 600 µg,  
800 µg, 1200 µg, and 1600 µg.

NDA: 20-747

Supplement Number: S-003

Therapeutic Classification: S

Date of Supplement: February 10, 1999

Date of Receipt: February 12, 1999

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Federal Food, Drug, and Cosmetic Act on April 13, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

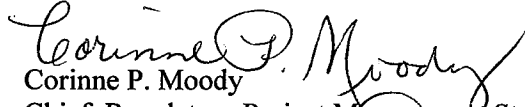
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthetic, Critical Care, and  
Addiction Drug Products  
Attention: Document Control Room, HFD-170  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 20-747/S-003

Page 2

If you have any questions, please contact Nancy Chamberlin, Regulatory Project Manager, at 301-827-7410.

Sincerely,

A handwritten signature in cursive script, reading "Corinne P. Moody". The signature is written in dark ink and is positioned above the printed name.

Corinne P. Moody

Chief, Regulatory Project Management Staff

Division of Anesthetic, Critical Care, and

Addiction Drug Products, HFD-170

Office of Drug Evaluation III

Center for Drug Evaluation and Research

NDA 20-747/S-003

Page 3

cc:

Original NDA 20747/S-003

HFD-170/Div. Files

HFD-170/CSO/Nancy Chamberlin

Drafted by: nc 3-25-99

Initialed by: C. P. Moody 3-26-99

Revised: 3-26-99nc

filename: A:\20747.03ltr.doc

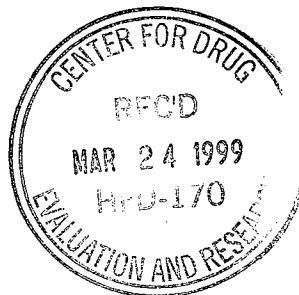
SUPPLEMENT ACKNOWLEDGEMENT

4745 Wiley Post Way Suite 650  
Salt Lake City, Utah 84116

Federal Express

March 23, 1999

NDA SUPPL AMEND  
SLR-003 BL  
ORIGINAL



Division of Anesthetic, Critical Care and  
Addiction Drug Products, HFD-170  
Attention: Document Control Room 9B23  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: NDA 20-747  
Actiq<sup>®</sup> (oral transmucosal fentanyl citrate, OTFC<sup>®</sup>)  
Risk Management Program - PC-Formatted Disks

Dear Sir/Madam:

Reference is made to the subject NDA, to our February 10, 1999, submission, and to a March 23, 1999, telephone conversation between Ms. Nancy Chamberlin, Project Manager (HFD-170), and Anesta personnel. During the referenced conversation, Ms. Chamberlin requested that Anesta submit a PC-formatted disk containing the FDA "approved" version of the Risk Management Program (RMP) dated November 4, 1998. This will enable the FDA to do their own DocuComp<sup>®</sup> comparison of the two RMPs (ie, compare the February 9, 1999, version, which was included in the February 10 submission, to the "approved" November 4, 1998, version).

As requested, PC-formatted disks containing a copy of the FDA "approved" RMP dated November 4, 1998, are provided. Please note that this particular RMP document represents the version faxed to Anesta on November 4, 1998, as part of the NDA approval letter. Both disks are located in the FDA archival (blue) copy of this submission (see page 19-002). If necessary, please refer to page 19-001 for instructions on how to compare two WORD documents.

If you have questions regarding this communication, please contact me by telephone (801.321.7456) or by facsimile (801.321.7490).

Sincerely,

Patricia J. Richards  
Director, Regulatory Affairs

cc: Nancy Chamberlin, Project Manager (HFD-170)  
Tom Willer, PhD, Abbott Laboratories

4745 Wiley Post Way Suite 650  
Salt Lake City, Utah 84116

Airborne Express

ORIGINAL

February 26, 1999

Cynthia G. McCormick, MD  
Director  
Division of Anesthetic, Critical Care and  
Addiction Drug Products, HFD-170  
Attention: Document Control Room 9B23  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: NDA 20-747  
Actiq® (oral transmucosal fentanyl citrate, OTFC®)  
Pricing

Dear Dr. McCormick:

Reference is made to Abbott Laboratories' letter dated January 22, 1999, and to a February 12, 1999, teleconference regarding the pricing structure for *Actiq*.

The purpose of this communication is to provide our rationale for the pricing of *Actiq* (see Section 19), and to also provide a revised pricing structure.

With the resolution of product pricing as contained in this submission, Anesta and Abbott are continuing to move forward towards launch. Much time has elapsed since our November approval, and *Actiq* needs to be made available soon for those patients who will benefit. We look forward to our teleconference on Monday, March 1, and to resolving all remaining issues as soon as possible thereafter.

If you have questions regarding this communication, please contact me by telephone (801.321.7456) or by facsimile (801.321.7490). Thank you.

Sincerely,

*Patricia J. Richards*

Patricia J. Richards  
Director, Regulatory Affairs

Encl.

cc: Nancy Chamberlin, Project Manager (HFD-170)  
Murray Lumpkin, MD, Deputy Director for Review Management (HFD-002)  
Tom Willer, PhD, Abbott Laboratories



*Filed on - March 1, 1999*  
*NJR*  
*8/11/99*

16 Pages has been withheld in full immediately following this page as  
B4 (CCI/TS)

p. 801 595 1405

f. 801 595 1406



4745 Wiley Post Way Suite 650  
Salt Lake City, Utah 84116

C  
NEW CORRESP  
ORIGINAL

NAT  
Nehombe  
6/21/99

Federal Express

February 10, 1999

Division of Anesthetic, Critical Care and  
Addiction Drug Products, HFD-170  
Attention: Document Control Room 9B23  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-747; Revised Risk Management Program  
Actiq® (oral transmucosal fentanyl citrate, OTFC®)

Dear Sir/Madam:

Reference is made to the November 4, 1998, approval letter for the Actiq NDA. Specific reference is made to your comments concerning any proposed change(s) in the current Actiq Risk Management Program (RMP), which is dated November 4, 1998. Since the RMP is considered an integral part of the approved NDA, we draw your attention to the revised RMP included in this submission. We trust that it will meet with your approval.

Included in Section 19 of this supplemental application is a copy of the revised RMP. The current RMP has been revised, for example, to reflect new information received from outside consultants, the deletion of information deemed to be proprietary by Abbott Laboratories (eg, the organizational structure within Abbott), and corrections relating to grammar and spelling. Also included in Section 19 is a "red-lined" copy of the RMP, which compares the revised RMP to the November 4, 1998, version (see page 19-078). Some of the key revisions are noted below.

Carton - Back Panel Text (Section 2.3)

Section 2.3 of the revised RMP includes a reference to the text appearing on the back panel of the shelf carton (see page 19-008). Due to the requirements related to production of Actiq, it was necessary to relocate some of the text on the back panel. Note that the prominent instructions on what to do in case of an accidental exposure were moved to the left hand side of the back panel (see page 19-035). It must be emphasized that the relocated text did not change.

It was also necessary to revise text appearing in this section of the RMP to reflect a request from the Division regarding the checklist for the pharmacist, which appears on the right hand side of the back panel. The checklist was updated to include the reminder that the patient should be counseled about disposal of partially consumed units (see pages 19-009 and 19-035).

On December 3, 1998, artwork reflecting the relocation of text on the carton was submitted to the Division for review and comment. Final printed labeling for the shelf carton (ie, for each dosage strength of Actiq) was included in a submission dated December 22, 1998.

Child-resistant Lock (Section 6.1)

Over the past several weeks, the Sponsor has had opportunities to learn more about likely patient acceptance of child-resistant cabinet locks. It has become clear that there are more common and potentially acceptable ways to provide secure bulk storage than the magnetic cabinet lock identified in Section 6.1 of the "original" Risk Management Program. Specifically, the Sponsor wishes to substitute a plastic latch/lock (known as a "double lock"--see page 19-019 of this submission for description). This is believed to be a better solution as the proposed plastic lock is more commonly used and will be more familiar to the patient population, which we believe would increase the probability of its use. In addition, the "key" portion of the magnetic lock could easily be lost, which would make all the medications stored within the cabinet inaccessible. This could cause serious problems for the patient.

Children's Booklet (Section 6.4)

Reference is made to the booklet designed by the National SAFEKIDS Campaign. Anesta has been advised that the booklet was developed at a 2nd to 4th (not 3rd) grade reading level. This correction has been incorporated into the revised RMP dated February 9, 1999 (see page 19-020).

Adverse Reactions (Section 8.3)

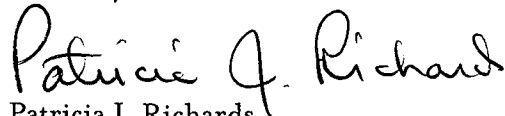
Section 8.3 of the RMP has been revised to reflect current procedures at Abbott Laboratories. The proposed revisions to Section 8.3.1 are intended to more accurately reflect the current adverse event investigation and follow-up process within Abbott Laboratories, Hospital Products Division. Please note that the revisions to Section 8.3 include the following:

- the reference to the schematic description of the "Incident Review Team" has been deleted, and
- the schematic itself have been deleted (eg, see RMP Attachment 7, Incident Team Schematic, included in the November 4, 1998, version).

For your convenience, Section 19 also includes a copy of the RMP dated November 4, 1998, and a PC-formatted disk containing a copy of the revised RMP dated February 9, 1999. It should be noted that the disk is located in the FDA archival (blue) copy of this submission (see page 19-205)

If you have questions regarding this submission, please contact me by telephone (801.595.1405) or by facsimile (801.321.7490).

Sincerely,



Patricia J. Richards  
Director, Regulatory Affairs

Enclosure

cc: Nancy Chamberlin, Project Manager, HFD-170  
Tom Willer, PhD, Abbott Laboratories