

Actiq[®]

(oral transmucosal fentanyl citrate)

Risk Management Program

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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
- *Actiq*'s CII status

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 Risk Management Plan and all of its components will 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 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 Figure 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 backside 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 (microgram content of active drug, product code, manufacturer 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.

Insert Figure 1

2.2 *Actiq* Child-Resistant Pouch

- See Figures 2 and 3.
- 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, 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. 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.

Insert Figures 2

Insert Figure 3

2.3 *Actiq* Shelf Carton

The *Actiq* shelf carton includes labeling messages targeting all three at-risk populations (Figures 4, 6 pages). 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, and to discuss the *Actiq* Welcome Kit. Below this space are prominent instructions on what to do in case of an accidental exposure. 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, and a reminder to read the *Actiq* Patient Leaflet. 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 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.

Insert Figure 4

Insert figure 5-1

Insert figure 5-2

Insert figure 5-3

Insert figure 5-4

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 carton 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 titration and 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)
- 100% drug accountability by individual count is required
- most stringent physical storage requirements
- no refills allowed, triplicate prescriptions may be required in some states
- registered pharmacist is required to ensure a legitimate medical purpose before dispensing

Actiq's status 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 three copies will be packaged in every shelf carton (RMP Attachment 1). 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 1-800 Poison Control 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 pain medicines . . .” is used.

3.3 Package Insert

The *Actiq* Package Insert (PI) [See RMP Attachment 2], clearly and explicitly communicates messages about child safety, proper patient selection and prevention of diversion and abuse (RMP Attachment 3). 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:

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 µg 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.

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.

- 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 have been described earlier in section 1.1 of this RMP:

- 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 2):

- Approximately 50 prominent physician educators in pain management
- Approximately 50 prominent nurse educators in pain management
- Approximately 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

Anesta and Abbott will publish articles, in peer-reviewed journals, messages that will reinforce elements of this RMP. The publications selected 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 (10,000)
- Journal of Clinical Oncology (circulation 20,000)
- Anesthesia and Analgesia (circulation 5,000)
- Seminars in Oncology (circulation 10,000)
- 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 incorporate the *Actiq* key safety messages and new product reviews 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
 - Rite Aid 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 *Actiq* Specialist (Abbott Sales Organization)

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

Each *Actiq* 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, *Actiq* Specialists will be tested prior to being certified to discuss *Actiq*.

In the approximately 3 months between product approval and product availability, the *Actiq* 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 *Actiq* 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 all 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 *Actiq* Specialists will direct them to promote into only the target audience.

In their personal calls to physicians, nurses, and pharmacists, the *Actiq* Specialist will demonstrate 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 RMP Attachment 7. This program will be available via mass direct mail, the *Actiq* 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 education and promotional materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed and the patient or 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 all patient education and promotional materials. Patients and caregivers will be instructed to call this number if *Actiq* has been inappropriately consumed, and the patient 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 magnetic lock to secure almost any existing household cabinet or drawer for the storage of *Actiq* and other medications (Figure 7).
- 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 (Figure 8).
- Child-Resistant 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 (Figure 9). 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 *Actiq* 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.

Insert Figure 7

Insert Figure 8

Insert Figure 9

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 *Actiq* 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 be understood by younger children will be distributed. This book has been developed at a 2nd to 3rd 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 all *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, *Actiq* warnings will be placed in the major commercial pharmacy precaution software 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 pharmacist warning screens and electronically produced patient information sheets are provided as RMP Attachment 7.

7.2 The *Actiq* Welcome Kit

This kit (previously described) will be personally presented to all targeted retail pharmacies by an *Actiq* 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 *Actiq* Specialists and be made available to any pharmacist upon request. The package 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 (e.g. 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, Anesta/Abbott will commit to substituting another potential supplier to broaden our sample in a timely manner.)

8.1 Direct Patient Feedback

8.1.1 Rite-Aid / Eckerd call back system

A callback 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 Rite-Aid, 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, Rite-Aid 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. This data provides the prescriber's name, the physician specialty and zip code. This 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 as RMP Attachment 6. 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.

Through its chargeback system, Abbott will receive information on retail pharmacy sales from drug wholesalers. This information will be shared with the *Actiq* Specialist. The *Actiq* 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 reinforce appropriate product usage and confirm the accuracy of the high volume *Actiq* pharmacy listing on which the *Actiq* Specialists are visiting. Information from the Abbott Trade Specialists' meetings with wholesalers will be shared with the *Actiq* 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 events 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.

All serious events, as defined by current federal regulations, receive immediate investigation and follow-up by Abbott. The details of this procedure are summarized below.

- a) The incident report is reviewed by the *Actiq* Incident Review Team and an action plan is developed. This group remains responsible for oversight of the process and for briefing senior management as the investigation proceeds.
- b) An investigation team is assigned and contact made with the reporting entity as soon as possible. On-site investigation is implemented if deemed necessary.
- c) The investigation team report conclusions are reported to the Incident Review Team, which consults with senior management to determine if corrective action should be recommended and/or taken.

A schematic of the Incident Review Team and process is attached as RMP Attachment 7.

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 (i.e., use by an individual other than for whom it was prescribed), whether or not the experiences 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" (i.e., that is used outside of the approved indication for *Actiq*) whether or not the experiences 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 Exposures Surveillance System (TESS)

TESS reports all contacts with U.S. Poison Control Centers. This database will be monitored for *Actiq* exposures. This data is 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. Any incident is investigated and resolved in conjunction with the DEA and state drug control authorities.

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 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 hospitals 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 *Actiq* 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 *Actiq* 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 revisions and approval before it is issued.
- 2) Prescribing patterns will be monitored for the physicians in question. If a problem persists, an *Actiq* 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 (i.e. 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 2 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 a serious child poisoning report, Abbott will initiate the standard operating procedure for adverse events detailed in section 8.3.1 of this RMP and in RMP Attachment 7.

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 Surveillance and Monitoring (OPDRA) 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 Section 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.

Figure 1
Actiq Unit

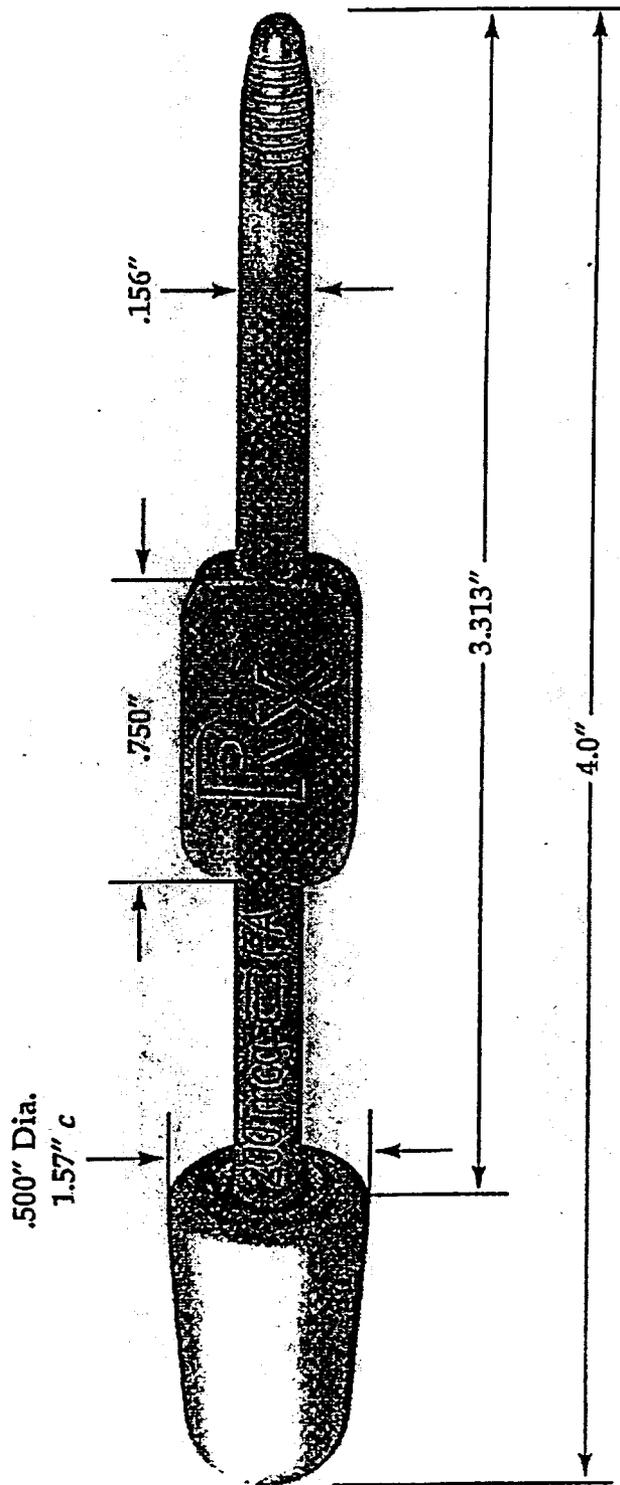


Figure 2

Pouch Front Panel

[ABBOTT LOGO]

1 Unit/NDC 0074-2461-24

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

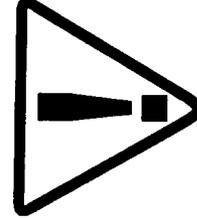
ACTIQ[®] equivalent to
400 mcg CII
(oral transmucosal fentanyl citrate) fentanyl base

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 in protective foil pouch at controlled room temperature 15° to 30° C (59° to 86°F) until ready to use.

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



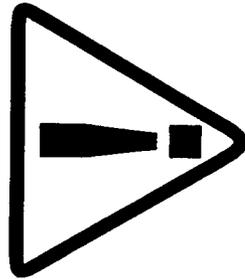
WARNING: Keep out of reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal.

19 1 012

Figure 3

Pouch Back Panel

In Box at Left of UPC Code:



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.

Figure 4

Shelf Carton Front Panel

[ABBOTT LOGO] 24 Units

NDC 0074-2461-24

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

ACTIQ[®]

(oral transmucosal fentanyl citrate)

equivalent to

400 mcg

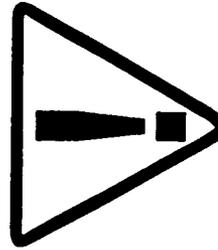
fentanyl base

Warning: May be habit forming.

CII

191

015



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.

Figure 4 (cont'd)

Shelf Carton Back Panel
Left Side

ACTIQ[®]**CII**

(oral transmucosal fentanyl citrate)

equivalent to

400 mcg

fentanyl base

**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.**

[Code]

Shelf Carton Back Panel **Right Side**

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

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.

Figure 4 (cont'd)

Shelf Carton Side Panel

[Abbott Logo] 24 Units

ACTIQ[®] CII
(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 in protective foil pouch at controlled room temperature 15° to 30°C (59° to 86°F) until ready to use.

Rx only

Figure 4 (cont'd)

Shelf Carton Side Panel

[Abbott Symbol] 24 Units

ACTIQ[®] CII

(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

19- 019

Figure 4 (cont'd)

Shelf Carton 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.

Figure 6
Child Safety Lock



Child-resistant lock

Figure 7: Secure Personal Container

Portable locking pouch



Figure 8
Child-Resistant Temporary Storage Bottle

Child-Resistant Temporary Storage Bottle

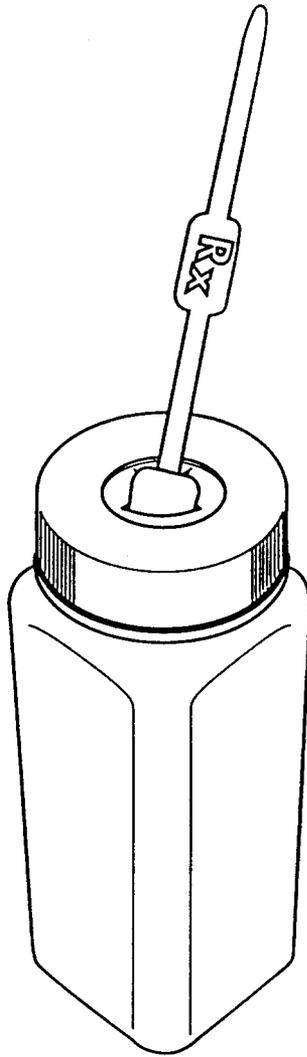


Figure 9
Home Warning Sticker/Refrigerator Magnet

Easel Placard or Magnetic Refrigerator Placard



Actiq® Emergency Information
WARNING: Keep out of the reach of children

- Immediately remove the medicine from the person's mouth (if possible) and save it for identification purposes.
- If the person is awake and alert, call **Poison Control at 1-800-XXX-YYYY**
- If the person is **NOT** awake and alert, keep them awake by shouting their name and shaking their arm or shoulder, and instructing them to breathe every 5-10 seconds. **Call 911 for emergency help.**
- If the person stops breathing, give mouth-to-mouth resuscitation until emergency help arrives.

Telephone Sticker (Decal type with bright color)



Actiq® Emergency Information
WARNING: Keep out of the reach of children

If someone accidentally takes *Actiq*, immediately remove the unit from their mouth
If they are awake and alert, call **Poison Control at 1-800-XXX-YYYY**
If the person is breathing very slowly, or not breathing at all, immediately
call 911 for emergency help.
Every 5-10 seconds until help arrives, shake them, shout their name and instruct them to breathe.

ATTACHMENTS

- RMP 1 *Actiq* Patient Leaflet
- RMP 2 *Actiq* Package Insert
- RMP 3 Elements of RMP to be Included in Speaker Bureau Training
- RMP 4 *Actiq* CD ROM schematic
- RMP 5 Pharmacy Computer Warning screens
- RMP 6 IMS National Disease and Therapeutic Index example page
- RMP 7 Incident Team schematic

Attachment 1

Actiq®
(oral transmucosal fentanyl citrate)

[Icon] **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-###-####.

WARNING: MAY BE HABIT FORMING

[Icon] **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 1-800-###-####.

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. If for some reason you are not finishing the entire unit each time you 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 direction 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.
- Actiq may cause some people to become sleepy, dizzy, or less alert. Discuss this with your doctor to get advice on whether it is safe for you to drive or operate machinery. Until you experienced how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc. 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.
3. 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-###-####.

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-###-####. If you still need help call your local Drug Enforcement Administration (DEA) office.

Warning: Keep out of the reach of children.

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

Printed in the USA

Sent to Anesta 11/4/98

Attachment 2

1
2
3 **Actiq®**
4 (oral transmucosal fentanyl citrate)
5 CII
6

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

10
11 *Actiq* is indicated only for the management of breakthrough
12 cancer pain in patients with malignancies who are already
13 receiving and who are tolerant to opioid therapy for their
14 underlying persistent cancer pain. Patients considered opioid tolerant
15 are those who are taking at least 60 mg morphine/day, 50 µg transdermal
16 fentanyl/hour, or an equianalgesic dose of another opioid for a week or
17 longer.

18
19 Because life-threatening hypoventilation could occur at any dose in
20 patients not taking chronic opiates, *Actiq* is contraindicated in the
21 management of acute or postoperative pain. This product **must not** be
22 used in opioid non-tolerant patients.

23
24 *Actiq* is intended to be used only in the care of cancer patients and only
25 by oncologists and pain specialists who are knowledgeable of and skilled
26 in the use of Schedule II opioids to treat cancer pain.

27
28 **Patients and their caregivers must be instructed that *Actiq* contains**
29 **a medicine in an amount which can be fatal to a child. Patients and**
30 **their caregivers must be instructed to keep all units out of the reach**
31 **of children and to discard opened units properly. (See Information**
32 **for Patients and Their Caregivers for disposal instructions.)**

33
34
35
36 **WARNING: May be habit forming**

37
38
39 **DESCRIPTION**

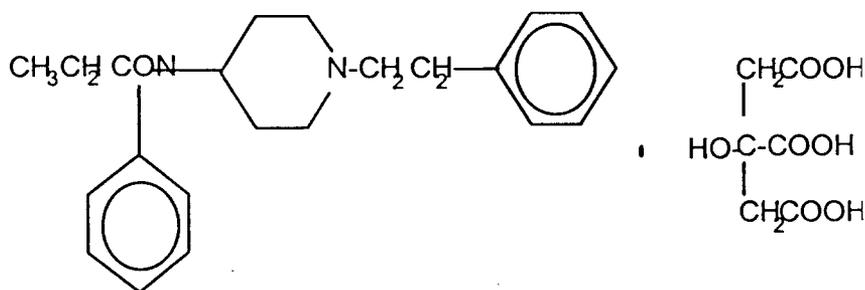
40 *Actiq* (oral transmucosal fentanyl citrate) is a solid formulation of
41 fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal
42 administration. *Actiq* is formulated as a white to off-white solid drug
43 matrix on a handle that is radiopaque and is fracture resistant (ABS
44 plastic) under normal conditions when used as directed.
45

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

50

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

58



59

60

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

64

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

67

68 CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

69

70 **Pharmacology:**

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

76

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

81

82 **Clinical Pharmacology**

83 **Analgesia:**

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

90

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

97

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

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

104

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

108

109 **Respiratory System:**

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

122

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

127

128 Fentanyl depresses the cough reflex as a result of its CNS activity.
129 Although not observed with *Actiq* in clinical trials, fentanyl given

130 rapidly by intravenous injection in large doses may interfere with
131 respiration by causing rigidity in the muscles of respiration. Therefore,
132 physicians and other healthcare providers should be aware of this
133 potential complication.

134

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

138

139 **Pharmacokinetics**

140 **Absorption:**

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

147

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

151

152 Normally, approximately 25% of the total dose of *Actiq* is rapidly
153 absorbed from the buccal mucosa and becomes systemically available.
154 The remaining 75% of the total dose is swallowed with the saliva and
155 then is slowly absorbed from the GI tract. About 1/3 of this amount
156 (25% of the total dose) escapes hepatic and intestinal first-pass
157 elimination and becomes systemically available. Thus, the generally
158 observed 50% bioavailability of *Actiq* is divided equally between rapid
159 transmucosal and slower GI absorption. Therefore, a unit dose of *Actiq*,
160 if chewed and swallowed, might result in lower peak concentrations and
161 lower bioavailability than when consumed as directed.

162

163 Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 µg)
164 has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl
165 levels following these four doses of *Actiq* are shown in Figure 1. The curves for each dose level
166 are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max}
167 and $AUC_{0 \rightarrow \infty}$ increased in a dose-dependent manner that is approximately proportional to the
168 *Actiq* administered.

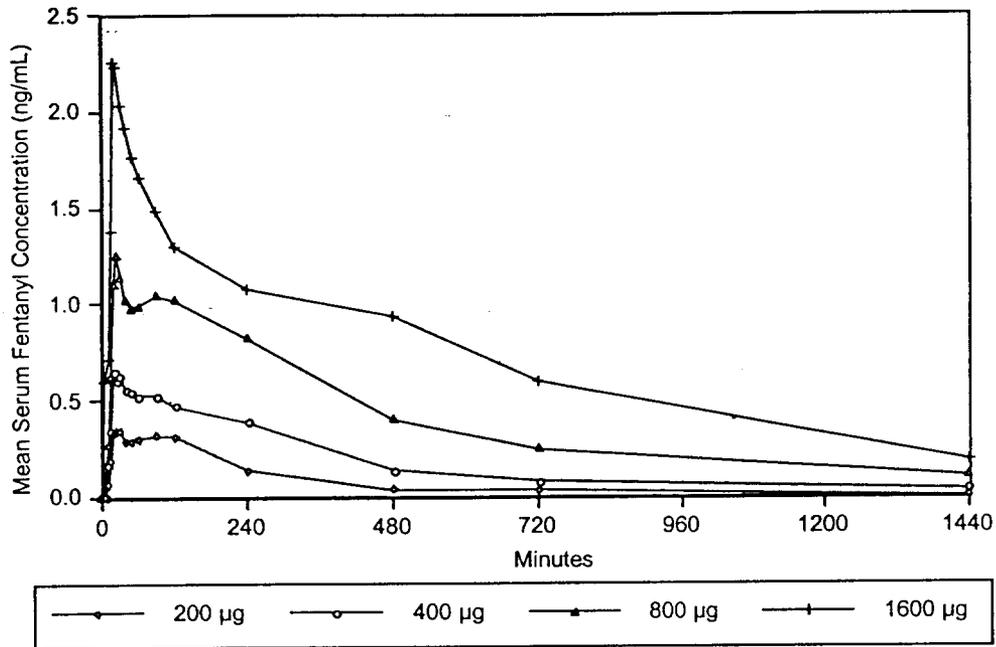
169

169 **Figure 1.**

170 **Mean Serum Fentanyl Concentration (ng/mL)**
171 **in Adult Subjects Comparing 4 doses of *Actiq***

172

173



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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 to 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 µg
Units of *Actiq*

Pharmacokinetic Parameter	200 µg	400 µg	800µg	1600 µg
T_{max} , minute median (range)	40 (20-120)	25 (20-240)	25 (20-120)	20 (20-480)
C_{max} , ng/mL mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440} , ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)

t_{1/2}, minute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

189

190 **Distribution:**

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

199

200 **Metabolism:**

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

205

206 **Elimination:**

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

215

216 **Special Populations:**

217 Elderly Patients:

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

226

227 Patients with Renal or Hepatic Impairment:

228 *Actiq* should be administered with caution to patients with liver or
 229 kidney dysfunction because of the importance of these organs in the

230 metabolism and excretion of drugs and effects on plasma-binding
231 proteins (see **PRECAUTIONS**).

232
233 Although fentanyl kinetics are known to be altered in both hepatic and
234 renal disease due to alterations in metabolic clearance and plasma
235 proteins, individualized doses of Actiq have been used successfully for
236 breakthrough cancer pain in patients with hepatic and renal disorders.
237 The duration of effect for the initial dose of fentanyl is determined by
238 redistribution of the drug, such that diminished metabolic clearance may
239 only become significant with repeated dosing or with excessively large
240 single doses. For these reasons, while doses titrated to clinical effect are
241 recommended for all patients, special care should be taken in patients
242 with severe hepatic or renal disease.

243
244 Gender

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

249
250 **CLINICAL TRIALS**

251
252 **Breakthrough Cancer Pain:**

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

260
261 In two dose titration studies 95 of 127 patients (75%) who were on
262 stable doses of either long-acting oral opioids or transdermal fentanyl for
263 their persistent cancer pain titrated to a successful dose of *Actiq* to treat
264 their breakthrough cancer pain within the dose range offered (200, 400,
265 600, 800, 1200 and 1600 µg). In these studies 11% of patients withdrew
266 due to adverse events and 14% withdrew due to other reasons. A
267 “successful” dose was defined as a dose where one unit of *Actiq* could
268 be used consistently for at least two consecutive days to treat
269 breakthrough cancer pain without unacceptable side effects.

270
271 The successful dose of *Actiq* for breakthrough cancer pain was not
272 predicted from the daily maintenance dose of opioid used to manage the
273 persistent cancer pain and is thus best determined by dose titration.

274

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

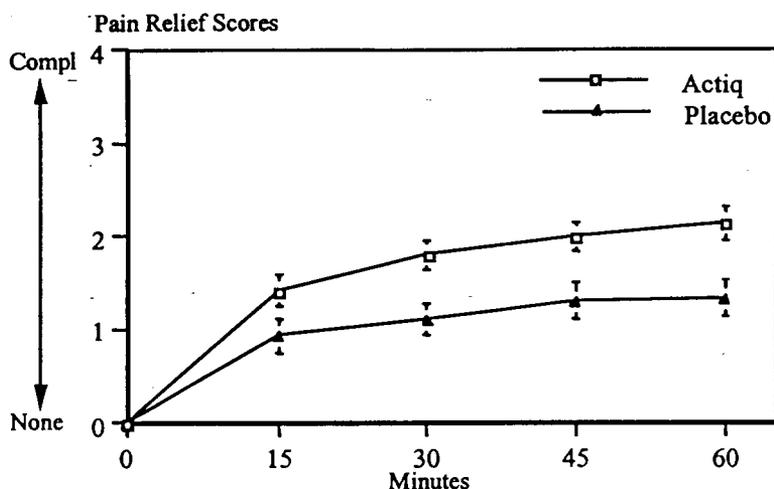
280
 281 **Table 2.**
 282 **Successful Dose of Actiq**
 283 **Following Initial Titration**

<i>Actiq</i> Dose	Total No (%) (N=92)
200 µg	13 (14)
400 µg	19 (21)
600 µg	14 (15)
800 µg	18 (20)
1200 µg	13 (14)
1600 µg	15 (16)
Mean ±SD	789±468 µg

284
 285
 286
 287
 288
 289
 290
 291
 292
 293
 294
 295
 296
 297 On average, patients over 65 years of age titrated to a mean dose that
 298 was about 200 µg less than the mean dose to which younger adult
 299 patients were titrated.

300
 301 *Actiq* produced statistically significantly more pain relief compared with
 302 placebo at 15, 30, 45 and 60 minutes following administration (see
 303 Figure 2).

304
 305 **Figure 2.**
 306 **Pain Relief (PR) Scores (Mean ± SD) During the**
 307 **Double-Blind Phase - All Patients With Evaluable**
 308 **Episodes on Both Actiq and Placebo (N=86)**
 309



Note to sponsor: Please revise your most recent submission- change the labels on the vertical scale from "worse" and "better" to "none" and "complete"; take out the footnotes, take out "imputed"

310
311
312
313
314
315
316
317

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."

318 **INDICATIONS AND USAGE**

319 (See **BOX WARNING** and **CONTRAINDICATIONS**)

320 *Actiq* is indicated only for the management of breakthrough cancer pain
321 in patients with malignancies who are **already receiving and who are**
322 **tolerant to opioid therapy for their underlying persistent cancer**
323 **pain.** Patients considered opioid tolerant are those who are taking at
324 least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an
325 equianalgesic dose of another opioid for a week or longer.

326
327 Because life-threatening hypoventilation could occur at any dose in
328 patients not taking chronic opiates, *Actiq* is contraindicated in the
329 management of acute or postoperative pain. This product **must not** be
330 used in opioid non-tolerant patients.

331
332 *Actiq* is intended to be used only in the care of cancer patients only by
333 oncologists and pain specialists who are knowledgeable of and skilled in
334 the use of Schedule II opioids to treat cancer pain.

335
336 *Actiq* should be individually titrated to a dose that provides adequate
337 analgesia and minimizes side effects. If signs of excessive opioid effects
338 appear before the unit is consumed, the dosage unit should be removed
339 from the patient's mouth immediately, disposed of properly, and

340 subsequent doses should be decreased (see **DOSAGE AND**
341 **ADMINISTRATION**).

342
343 Patients and their caregivers must be instructed that *Actiq* contains a
344 medicine in an amount that can be fatal to a child. Patients and their
345 caregivers must be instructed to keep all units out of the reach of
346 children and to discard opened units properly in a secured container.

347

348 **CONTRAINDICATIONS**

349 Because life-threatening hypoventilation could occur at any dose in
350 patients not taking chronic opiates, *Actiq* is contraindicated in the
351 management of acute or postoperative pain. The risk of respiratory
352 depression begins to increase with fentanyl plasma levels of 2.0 ng/mL
353 in opioid non-tolerant individuals (See **Pharmacokinetics**). This
354 product **must not** be used in opioid non-tolerant patients.

355

356 Patients considered opioid tolerant are those who are taking at least 60
357 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic
358 dose of another opioid for a week or longer.

359

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

362

363 **WARNINGS**

364 See **BOX WARNING**

365

366 The concomitant use of other CNS depressants, including other opioids,
367 sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers,
368 skeletal muscle relaxants, sedating antihistamines, potent inhibitors of
369 cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and
370 certain protease inhibitors), and alcoholic beverages may produce
371 additive depressant effects. Hypoventilation, hypotension, and profound
372 sedation may occur.

373

374 *Actiq* is not recommended for use in patients who have received MAO
375 inhibitors within 14 days, because severe and unpredictable potentiation
376 by MAO inhibitors has been reported with opioid analgesics.

377

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

381

382 **Patients and their caregivers must be instructed that *Actiq* contains**
383 **a medicine in an amount, which can be fatal to a child.** Patients and
384 their caregivers must be instructed to keep both used and unused dosage
385 units out of the reach of children. While all units should be disposed of

386 immediately after use, partially consumed units represent a special risk
387 to children. In the event that a unit is not completely consumed it must
388 be properly disposed as soon as possible. (See **SAFETY AND**
389 **HANDLING; PRECAUTIONS, and PATIENT PACKAGE INSERT**
390 for specific patient instructions).

391
392 Physicians and dispensing pharmacists must specifically question
393 patients or caregivers about the presence of children in the home on a
394 full time or visiting basis and counsel them regarding the dangers to
395 children from inadvertent exposure.

396 397 **PRECAUTIONS**

398 **General**

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

402
403 Opioid analgesics impair the mental and/or physical ability required for
404 the performance of potentially dangerous tasks (e.g., driving a car or
405 operating machinery). Patients taking *Actiq* should be warned of these
406 dangers and should be counseled accordingly.

407
408 The use of concomitant CNS active drugs requires special patient care
409 and observation. (See **WARNINGS.**)

410 411 **Hypoventilation (Respiratory Depression)**

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

417 418 **Chronic Pulmonary Disease**

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

425 426 **Head Injuries and Increased Intracranial Pressure**

427 *Actiq* should only be administered with extreme caution in patients who
428 may be particularly susceptible to the intracranial effects of CO₂
429 retention such as those with evidence of increased intracranial pressure
430 or impaired consciousness. Opioids may obscure the clinical course of a

431 patient with a head injury and should be used only if clinically
432 warranted.

433
434 **Cardiac Disease**

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

437
438 **Hepatic or Renal Disease**

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

443
444 **Information for Patients and Their Caregivers**

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

453
454 Patients and their caregivers should be provided with an *Actiq* Welcome
455 Kit, which contains educational materials and safe storage containers to
456 help patients store *Actiq* and other medicines out of the reach of children.
457 Patients and their caregivers should also have an opportunity to watch
458 the patient safety video, which provides proper product use, storage,
459 handling and disposal directions. Patient should also have an
460 opportunity to discuss the video with their health care providers. Health
461 care professionals should call 1-800-xxx-xxxx to obtain a supply of
462 welcome kits or videos for patient viewing.

463
464 **Disposal of used *Actiq* units**

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

- 467
468 1) After consumption of the unit is complete and the matrix is totally
469 dissolved, throw away the handle in a trash container that is out of
470 the reach of children.
471
472 2) If any of the drug matrix remains on the handle, place the handle
473 under hot running tap water until all of the drug matrix is dissolved,
474 and then dispose of the handle in a place that is out of the reach of
475 children.

476

477 3) Handles in the child-resistant container should be disposed of (as
478 described in steps 1 and 2) at least once a day.

479

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

485

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

487

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

491

492 To dispose of the unused *Actiq* units:

493

494 1) Remove the *Actiq* unit from its pouch using scissors, and hold the
495 *Actiq* by its handle over the toilet bowl.

496

497 2) Using wire-cutting pliers cut off the drug matrix end so that it falls
498 into the toilet.

499

500 3) Dispose of the handle in a place that is out of the reach of children.

501

502 4) Repeat steps 1, 2, and 3 for each *Actiq* unit. Flush the toilet twice
503 after 5 units have been cut and deposited into the toilet.

504

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

508

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

514

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

519

520 **Laboratory Tests**

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

522

523 **Drug Interactions**

524 See WARNINGS.

525

526 Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl
527 by the cytochrome P450 3A4 isoform. Drugs that inhibit P450 3A4
528 activity may increase the bioavailability of swallowed fentanyl (by
529 decreasing intestinal and hepatic first pass metabolism) and may
530 decrease the systemic clearance of fentanyl. The expected clinical
531 results would be increased or prolonged opioid effects. Drugs that
532 induce cytochrome P450 3A4 activity may have the opposite effects.
533 However, no *in vitro* or *in vivo* studies have been performed to assess the
534 impact of those potential interactions on the administration of *Actiq*.
535 Thus patients who begin or end therapy with potent inhibitors of
536 CYP450 3A4 such as macrolide antibiotics (e.g., erythromycin), azole
537 antifungal agents (e.g., ketoconazole and itraconazole), and protease
538 inhibitors (e.g., ritanovir) while receiving *Actiq* should be monitored for
539 a change in opioid effects and, if warranted, the dose of *Actiq* should be
540 adjusted.

541

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

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

545

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

551

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

556

557 **Pregnancy - Category C**

558 Fentanyl has been shown to impair fertility and to have an embryocidal
559 effect with an increase in resorptions in rats when given for a period of
560 12 to 21 days in doses of 30 µg/kg IV or 160 µg/kg subcutaneously.

561

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

567

568 **Labor and Delivery**

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

570

571 **Nursing Mothers**

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

575

576 **Pediatric Use**

577 See WARNINGS

578

579 **Geriatric Use**

580 Of the 257 patients in clinical studies of *Actiq* in breakthrough cancer
581 pain, 61 (24%) were 65 and over, while 15 (6%) were 75 and over.

582

583 Those patients over the age of 65 titrated to a mean dose that was about
584 200 µg less than the mean dose titrated to by younger patients. Previous
585 studies with intravenous fentanyl showed that elderly patients are twice
586 as sensitive to the effects of fentanyl as the younger population.

587

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

593

594

595 **ADVERSE REACTIONS**

596 Pre-Marketing Clinical Trial Experience

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

601

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

606

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

611

612 Because the clinical trials of *Actiq* were designed to evaluate safety and
613 efficacy in treating breakthrough cancer pain, all patients were also
614 taking concomitant opioids, such as sustained-release morphine or

615 transdermal fentanyl, for their persistent cancer pain. The adverse event
 616 data presented here reflect the actual percentage of patients experiencing
 617 each adverse effect among patients who received *Actiq* for breakthrough
 618 cancer pain along with a concomitant opioid for persistent cancer pain.
 619 There has been no attempt to correct for concomitant use of other
 620 opioids, duration of *Actiq* therapy, or cancer-related symptoms. Adverse
 621 events are included regardless of causality or severity.

622
 623 Three short-term clinical trials with similar titration schemes were
 624 conducted in 257 patients with malignancy and breakthrough cancer
 625 pain. Data are available for 254 of these patients. The goal of titration
 626 in these trials was to find the dose of *Actiq* that provided adequate
 627 analgesia with acceptable side effects (successful dose). Patients were
 628 titrated from a low dose to a successful dose in a manner similar to
 629 current titration dosing guidelines. Table 3 lists by dose groups, adverse
 630 events with an overall frequency of 1% or greater that occurred during
 631 titration and are commonly associated with opioid administration or are
 632 of particular clinical interest. The ability to assign a dose-response
 633 relationship to these adverse events is limited by the titration schemes
 634 used in these studies. Adverse events are listed in descending order of
 635 frequency within each body system.

636
 637
 638
 639
 640
 641
 642

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)

Dose Group	200- 600 µg	800- 1400 µg	1600 µg	>1600 µg	Any
Number Of Patients	230	138	54	41	254
Body As A Whole					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2
Digestive					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17

Somnolence	9	9	11	20	17
Confusion	1	6	2	0	4
Anxiety	3	0	2	0	3
Abnormal Gait	0	1	4	0	2
Dry Mouth	1	1	2	0	2
Nervousness	1	1	0	0	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

643

644

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.

645

646

647

648

Body as a Whole:

649

Pain, fever, abdominal pain, chills, back pain, chest pain, infection

650

Cardiovascular:

651

Migraine

652

653

Digestive:

654

Diarrhea, dyspepsia, flatulence

655

Metabolic and Nutritional:

656

Peripheral edema, dehydration

657

Nervous:

658

Hypesthesia

659

Respiratory:

660

Pharyngitis, cough increased

661

662

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.

663

664

665

Body as a Whole:

666

Flu syndrome, abscess, bone pain

667

Cardiovascular:

668

Deep thrombophlebitis, hypertension, hypotension

669

Digestive:

670 Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth
 671 ulceration, oral moniliasis
 672 Hemic and Lymphatic:
 673 Anemia, leukopenia
 674 Metabolic and Nutritional:
 675 Edema, hypercalcemia, weight loss
 676 Musculoskeletal:
 677 Myalgia, pathological fracture, myasthenia
 678 Nervous:
 679 Abnormal dreams, urinary retention, agitation, amnesia, emotional lability, euphoria,
 680 incoordination, libido decreased, neuropathy, paresthesia, speech disorder
 681 Respiratory:
 682 Hemoptysis, pleural effusion, rhinitis, asthma, hiccup, pneumonia, respiratory
 683 insufficiency, sputum increased
 684 Skin and Appendages:
 685 Alopecia, exfoliative dermatitis
 686 Special Senses:
 687 taste perversion
 688 Urogenital:
 689 Vaginal hemorrhage, dysuria, hematuria, urinary incontinence, urinary tract infection

690
 691 A long-term extension study was conducted in 156 patients with malignancy and breakthrough
 692 cancer pain who were treated for an average of 129 days. Data are available for 152 of these
 693 patients. Table 4 lists by dose groups, adverse events with an overall frequency of 1% or greater
 694 that occurred during the long-term extension study and are commonly associated with opioid
 695 administration or are of particular clinical interest. Adverse events are listed in descending order
 696 of frequency within each body system.
 697

698 **Table 4.**
 699 **Percent of Patients with Adverse Events Commonly Associated with**
 700 **Opioid Administration or of Particular Clinical Interest Which**
 701 **Occurred During Long Term Treatment**
 702 **(Events in 1% or more of Patients)**

703

Dose Group	200- 600 µg	800- 1400 µg	1600 µg	>1600 µg	Any
Number Of Patients	98	83	53	27	152
Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	9

Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	36	25	26	45
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anxiety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confusion	2	5	13	7	10
Depression	9	4	2	7	9
Insomnia	5	1	8	4	7
Abnormal Gait	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	0	4	3
Stupor	4	1	0	0	3
Vasodilatation	1	1	4	0	3
Thinking Abnormal	2	1	0	0	2
Abnormal Dreams	1	1	0	0	1
Convulsion	0	1	2	0	1
Myoclonus	0	0	4	0	1
Tremor	0	1	2	0	1
Vertigo	0	0	4	0	1
Respiratory					
Dyspnea	15	16	8	7	22
Skin					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

704
705
706
707
708
709

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:

710 Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection,
711 abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection,
712 cachexia, cellulitis, malaise, pelvic pain
713 Cardiovascular:
714 Deep thrombophlebitis, migraine, palpitation, vascular disorder
715 Digestive:
716 Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal
717 disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice,
718 periodontal abscess, eructation, glossitis, rectal hemorrhage
719 Hemic and Lymphatic:
720 Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema,
721 pancytopenia
722 Metabolic and Nutritional:
723 Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia,
724 hypercalcemia, hypomagnesemia
725 Musculoskeletal:
726 Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder
727 Nervous:
728 Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder
729 Respiratory:
730 Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma,
731 hemoptysis, sputum increased
732 Skin and Appendages:
733 Skin ulcer, alopecia
734 Special Senses:
735 Tinnitus, conjunctivitis, ear disorder, taste perversion
736 Urogenital:
737 Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal
738 edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast
739 neoplasm, vaginal hemorrhage, vaginitis
740

741 The following events occurred with a frequency of less than 1% in the long-term extension study
742 and are listed in descending order of frequency within each body system.
743

744 Body as a Whole:

745 Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection
746 site pain, mucous membrane disorder, neck rigidity
747 Cardiovascular:
748 Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural
749 hypotension, tachycardia
750 Digestive:
751 Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum
752 hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries,
753 tooth disorder
754 Hemic and Lymphatic:
755 Bleeding time increased

756 Metabolic and Nutritional:
757 Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia,
758 hypoproteinemia, thirst
759 Musculoskeletal:
760 Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder
761 Nervous:
762 Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop,
763 hallucinations, hemiplegia, miosis, subdural hematoma
764 Respiratory:
765 Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice
766 alteration
767 Skin and Appendages:
768 Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash
769 Special Senses:
770 Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial
771 transitory deafness
772 Urogenital:
773 Kidney pain, nocturia, oliguria, polyuria, pyelonephritis
774

775 DRUG ABUSE AND DEPENDENCE

776 Fentanyl is a mu-opioid agonist and a Schedule II controlled substance
777 that can produce drug dependence of the morphine type. *Actiq* may be
778 subject to misuse, abuse and addiction.
779

780 The administration of *Actiq* should be guided by the response of the
781 patient. Physical dependence, per se, is not ordinarily a concern when
782 one is treating a patient with chronic cancer pain, and fear of tolerance
783 and physical dependence should not deter using doses that adequately
784 relieve the pain.
785

786 Opioid analgesics may cause physical dependence. Physical dependence
787 results in withdrawal symptoms in patients who abruptly discontinue the
788 drug. Withdrawal also may be precipitated through the administration of
789 drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or
790 mixed agonist/antagonist analgesics (pentazocine, butorphanol,
791 buprenorphine, nalbuphine).
792

793 Physical dependence usually does not occur to a clinically significant
794 degree until after several weeks of continued opioid usage. Tolerance, in
795 which increasingly larger doses are required in order to produce the
796 same degree of analgesia, is initially manifested by a shortened duration
797 of analgesic effect, and subsequently, by decreases in the intensity of
798 analgesia.
799

800 The handling of *Actiq* should be managed to minimize the risk of
801 diversion, including restriction of access and accounting procedures as

802 appropriate to the clinical setting and as required by law (see **SAFETY**
803 **AND HANDLING**).

804 **OVERDOSAGE**

806 **Clinical Presentation**

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

812 **General**

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

818 **Treatment of Overdosage (Accidental Ingestion) in the Opioid** 820 **NON-Tolerant Person**

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

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

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

834 **General Considerations for Overdose**

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

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

843 Although muscle rigidity interfering with respiration has not been seen
844 following the use of *Actiq*, this is possible with fentanyl and other
845

848 opioids. If it occurs, it should be managed by the use of assisted or
849 controlled ventilation, by an opioid antagonist, and as a final alternative,
850 by a neuromuscular blocking agent.

851

852 **DOSAGE AND ADMINISTRATION**

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

854

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

857

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

862

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

867

868 **Administration of *Actiq***

869 The foil package should be opened with scissors immediately prior to
870 product use. The patient should place the *Actiq* unit in his or her mouth
871 between the cheek and lower gum, occasionally moving the drug matrix
872 from one side to the other using the handle. The *Actiq* unit should be
873 sucked, not chewed. A unit dose of *Actiq*, if chewed and swallowed,
874 might result in lower peak concentrations and lower bioavailability than
875 when consumed as directed.

876

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

882

883 **Patients and caregivers must be instructed that *Actiq* contains**
884 **medicine in an amount that could be fatal to a child.** While all units
885 should be disposed of immediately after use, partially used units
886 represent a special risk and must be disposed of as soon as they are
887 consumed and/or no longer needed. Patients and caregivers should be
888 advised to dispose of any units remaining from a prescription as soon as
889 they are no longer needed (see **Disposal Instructions**).

890

891 **Dose Titration**

892 **Starting Dose:** The *initial dose of Actiq to treat episodes of breakthrough*
893 *cancer pain should be 200 µg.* Patients should be prescribed an initial

894 titration supply of six 200- μ g *Actiq* units, thus limiting the number of
895 units in the home during titration. Patients should use up all units before
896 increasing to a higher dose.

897
898 From this initial dose, patients should be closely followed and the
899 dosage level changed until the patient reaches a dose that provides
900 adequate analgesia using a single *Actiq* dosage unit per breakthrough
901 cancer pain episode.

902
903 Patients should record their use of *Actiq* over several episodes of
904 breakthrough cancer pain and review their experience with their
905 physicians to determine if a dosage adjustment is warranted.

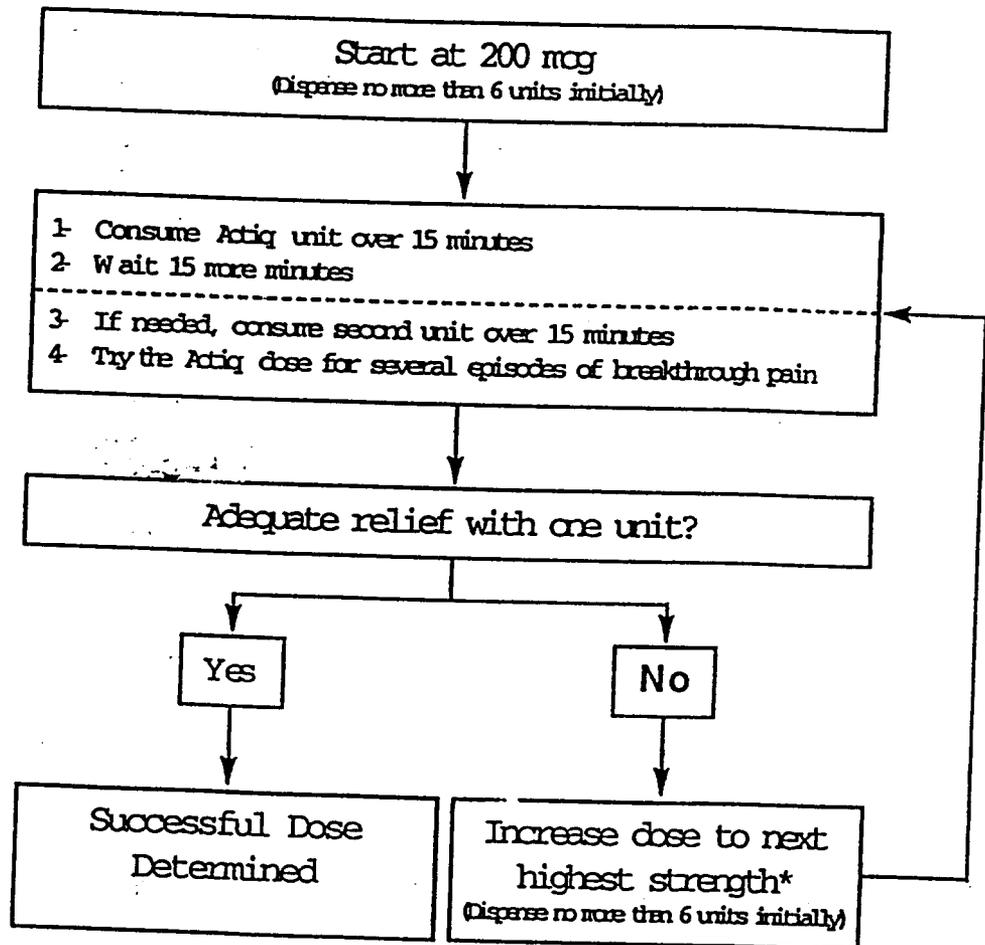
906
907 Redosing within a single episode: Until the appropriate dose is reached,
908 patients may find it necessary to use an additional *Actiq* unit during a
909 single episode. Redosing may start 15 minutes after the previous unit
910 has been completed (30 minutes after the start of the previous unit).
911 While patients are in the titration phase and consuming units which
912 individually may be subtherapeutic, no more than two units should be
913 taken for each individual breakthrough cancer pain episode.

914
915 Increasing the dose: If treatment of several consecutive breakthrough
916 cancer pain episodes requires more than one *Actiq* per episode, an
917 increase in dose to the next higher available strength should be
918 considered. At each new dose of *Actiq* during titration, it is
919 recommended that six units of the titration dose be prescribed. Each
920 new dose of *Actiq* used in the titration period should be evaluated over
921 several episodes of breakthrough cancer pain (generally 1-2 days) to
922 determine whether it provides adequate efficacy with acceptable side
923 effects. The incidence of side effects is likely to be greater during this
924 initial titration period compared to later, after the effective dose is
925 determined.

926
927 Daily Limit: Once a successful dose has been found (i.e., an average
928 episode is treated with a single unit), patients should limit consumption
929 to four or fewer units per day. If consumption increases above four
930 units/day, the dose of the long-acting opioid used for persistent cancer
931 pain should be re-evaluated.

Actiq Titration Process

See Box Warning



*Available dosage strengths include: 200, 400, 600, 800, 1200, and 1600 mg.

DRAFT

933 **Dosage Adjustment**

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

939
940 Generally, the *Actiq* dose should be increased when patients require
941 more than one dosage unit per breakthrough cancer pain episode for
942 several consecutive episodes. When titrating to an appropriate dose
943 small quantities (six units) should be prescribed at each titration step.
944 Physicians should consider increasing the around-the-clock opioid dose
945 used for persistent cancer pain in patients experiencing more than four
946 breakthrough cancer pain episodes daily.

947 948 **Discontinuation of *Actiq***

949
950 For patients requiring discontinuation of opioids, a gradual downward
951 titration is recommended because it is not known at what dose level the
952 opioid may be discontinued without producing the signs and symptoms
953 of abrupt withdrawal.

954 955 **SAFETY AND HANDLING**

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

961
962 Store at 25°C (77°F) with excursions permitted between 15 and 30°C
963 (59°-86° F) until ready to use. (See USP Controlled Room
964 Temperature.)

965
966 *Actiq* should be protected from freezing and moisture. Do not store
967 above 25°C. Do not use if the foil pouch has been opened.

968 969 **DISPOSAL OF *ACTIQ***

970
971 Patients must be advised to dispose of any units remaining from a
972 prescription as soon as they are no longer needed. While all units should
973 be disposed of immediately after use, partially consumed units represent
974 a special risk because they are no longer protected by the child resistant
975 pouch, yet may contain enough medicine to be fatal to a child (see
976 **Information for Patients**).

977

DRAFT

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

983
984 Patients and members of their household must be advised to dispose of
985 any units remaining from a prescription as soon as they are no longer
986 needed. Instructions are included in **Information for Patients and**
987 **Their Caregivers** and in the patient leaflet. If additional assistance is
988 required, referral to the *Actiq* 800# (1-800-xxx-xxxx) should be made.

989
990 **HOW SUPPLIED**

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

995
996 Patients should be prescribed an initial titration supply of six 200- μ g
997 *Actiq* units. At each new dose of *Actiq* during titration, it is
998 recommended that only six units of the next higher dose be prescribed.

999
1000 Each dosage unit has a white to off-white color. The dosage strength of
1001 each unit is marked on the handle, the foil pouch and the carton. See foil
1002 pouch and carton for product information.

1003

1004	Dosage Strength	Carton/Foil	
1005	<u>(fentanyl base)</u>	<u>Pouch Color</u>	<u>NDC Number</u>
1006			
1007	200 μ g	Gray	NDC 0074-2460-01
1008	400 μ g	Blue	NDC 0074-2461-01
1009	600 μ g	Orange	NDC 0074-2462-01
1010	800 μ g	Purple	NDC 0074-2463-01
1011	1200 μ g	Green	NDC 0074-2464-01
1012	1600 μ g	Burgundy	NDC 0074-2465-01

1013
1014 **Note: Colors are a secondary aid in product identification. Please be sure**
1015 **to confirm the printed dosage before dispensing.**

1016
1017 Rx only.

1018
1019 DEA order form required. A Schedule CII narcotic.

1020
1021 Manufactured by ABBOTT LABORATORIES, NORTH CHICAGO, IL
1022 60064, USA.

DRAFT

1023 Distributed by ABBOTT LABORATORIES, INC., NORTH
024 CHICAGO, IL 60064, USA.
1025
1026 Under license from ANESTA CORP., Salt Lake City, UT 84116, USA
1027 U. S. Patent No. 4,671,953
1028 Printed in USA
1029
1030 Sent to Anesta 11-04-98

Attachment 3

RMP 3
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 4



RMP 4
Actiq CD ROM schematic

COPY

Abbott HFD
ACTIQ CD-ROM--Module
G & A Job #: AB 6313
Abbott Project #: 96-52EC
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

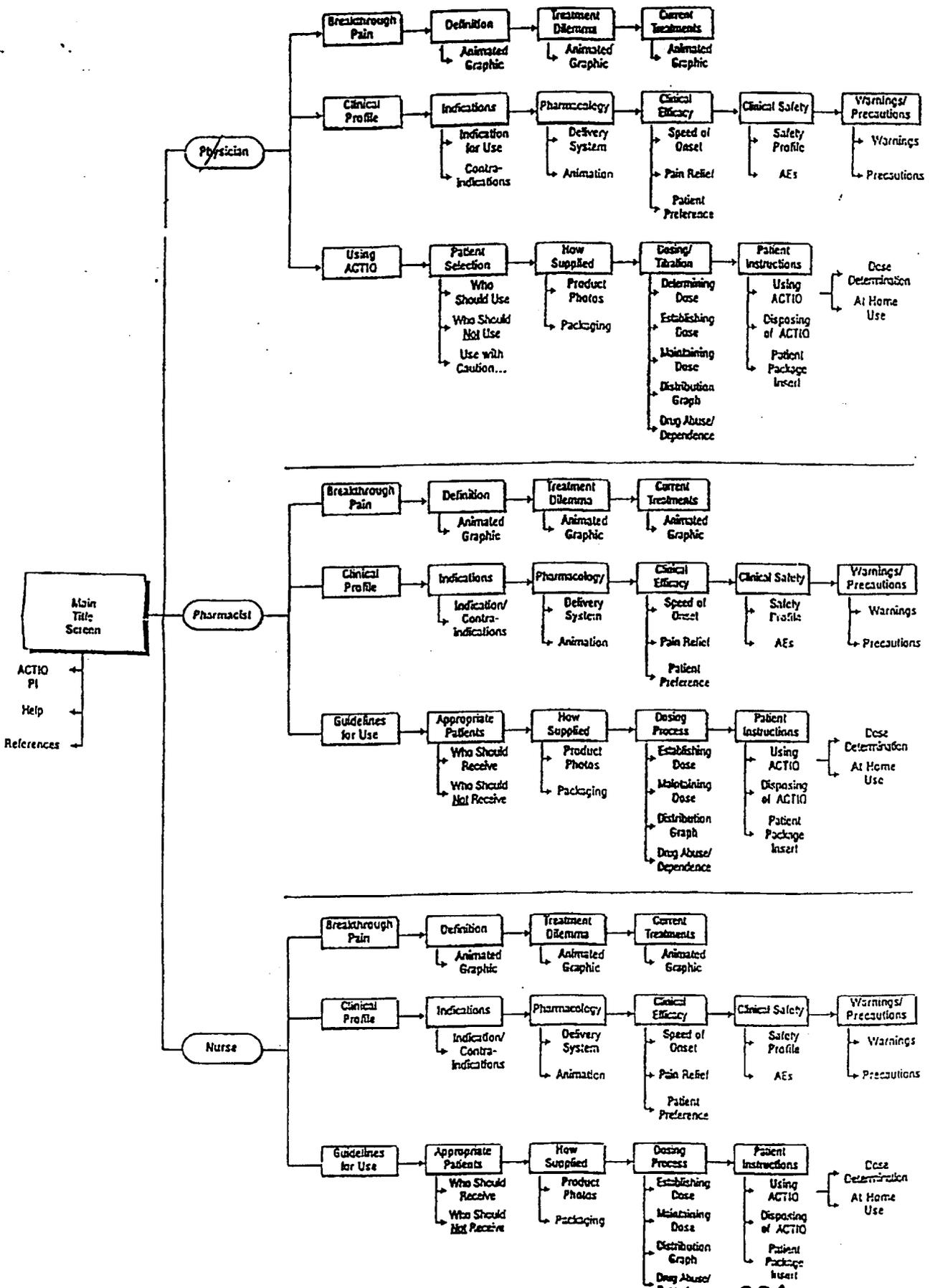
Physician

Pharmacist

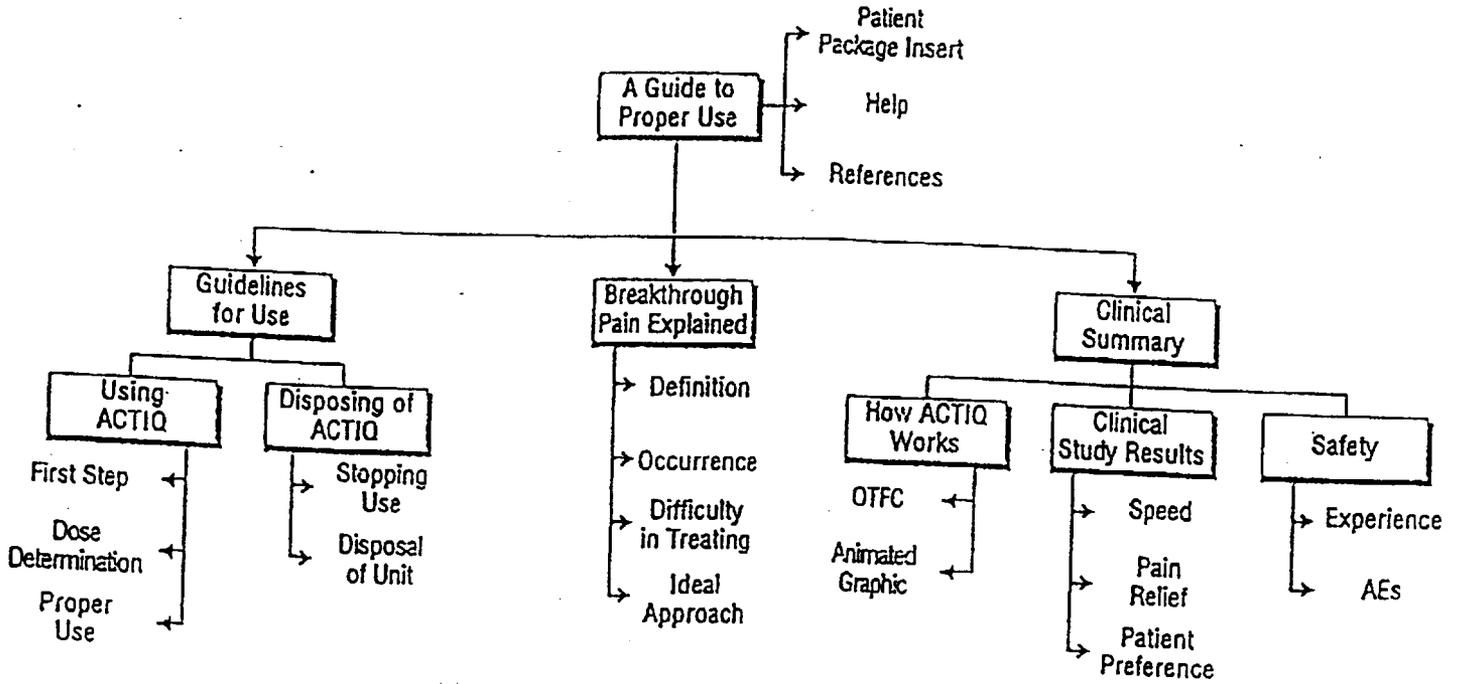


Attachment 5

CD-ROM



Patient CD-ROM



RMF 5

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 mg, #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.**

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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 6

RMP 6

IMS National Disease and Therapeutic Index Example Page

EST. U.S. APPEARANCES (000) SAMPLE DATA DRUG APPEARANCES DRUG USES	12 MONTHS		CURR QTR 158	MS-CONTIN	142443 PURVE FR CLASS 02722	PAGE 243
	CURR	PRIOR				
	638	617				
	239	257	57		CURRENT QTR: 4661	
	234	253	53		CURRENT 12 MNS: JAN 85-DEC 85	

APPEARANCES (000)	CURRENT 12 MONTHS				CURRENT QTR		APPEARANCES (000)	CURRENT 12 MONTHS					
	NO	%	PHYS/ YEAR	ALL DRUGS	APP	PEN		TOTAL NO	%	MALE NO	%	FEMALE NO	%
PHYSICIAN SPECIALTY	638	100	7	100	100	1	PATIENT AGE	601	100	272	100	329	100
ALLERGY	-	-	-	1	-	-	2 & UNDER	-	-	-	-	-	-
ALL OTHER SURGERY	37	3	1	1	0	1	3-9	-	-	-	-	-	-
CARDIOLOGY	10	2	1	5	4	1	10-19	1	0	-	-	-	-
COLON/RECT SURGERY	-	-	-	0	-	-	20-29	86	14	45	17	41	12
DERMATOLOGY	-	-	-	2	-	-	30-39	152	27	85	25	83	23
EMERGENCY MEDICINE	-	-	-	2	-	-	40-49	41	7	21	8	20	6
EAR/NOSE/THROAT	-	-	-	1	-	-	50-59	208	35	67	22	121	37
FAMILY PRACTICE	41	7	1	14	17	2	60-69	88	15	43	16	45	14
GASTROENTEROLOGY	2	0	0	2	1	1	70-79	75	2	7	3	8	2
GENERAL PRACTICE	3	0	0	5	-	-	80+	-	-	-	-	-	-
GENERAL SURGERY	36	8	3	3	7	1	2 M/F	100	-	45	-	55	-
INTERNAL MEDICINE	176	28	3	22	19	1	BRUG USES (000)						
ENDOCRINOLOGY	-	-	-	1	-	-							
GERIATRICS	2	0	4	0	-	-							
INTERNAL MEDICINE	153	24	3	13	14	1							
PULMONARY DISEASE	14	2	3	2	-	-							
RHEUMATOLOGY	3	1	2	1	0	1							
NEUROLOGY	8	1	1	1	3	2							
OBSTETRICS/GYNECOL	-	-	-	6	-	-	DIAGNOSES	651	100	100	100		
ONCOLOGY	259	40	35	2	42	20	02 NEOPLASMS	399	61	1	-	71	63
HEMATOLOGY	30	5	27	0	4	19	1625 MAL NEO BRONCH-LUNG UNSP	111	17	-4	139	17	12
ONCOLOGY	221	35	31	1	34	21	1748 MAL NEO FEM BREAST UNSP	39	6	1	41	5	5
OPHTHALMOLOGY	-	-	-	3	-	-	1539 MAL NEO COLON UNSPEC	37	6	2	71	3	3
ORTHOPEDIC SURGERY	45	7	3	2	2	1	1250 MALIGN NEO OF PROSTATE	24	4	1	55	8	1
ORTHOPEDIC MFO	3	1	0	7	3	1	1530 MAL NEO DISSEMINATED	21	3	1	17	3	4
OBSTETRICS	-	-	-	11	-	-	1578 MAL NEO PANCREAS UNS	15	2	4	14	3	1
PSYCHIATRY	6	1	0	4	-	-	2030 MULTIPLE MYELOMA	13	2	3	16	1	2
UROLOGY	3	1	1	2	-	-	8716 MAL NEO SITE UNS CON TIS	12	2	4	19	1	2
NEPHROLOGY	-	-	-	1	-	-	1831 OTH MAL NEO NO SPEC SITE	11	2	1	1	1	3
UROLOGY	5	1	1	1	-	-	1845 MALIGN BONE-MARROW	11	2	1	1	1	3
							1723 MAL MEL SKIN UNSP SITE	10	1	2	16	3	4
							2003 LYMPHOMAS OTHER	8	1	1	34	1	4
PHYSICIAN AGE	638	100	2	100	100	1	1408 MAL NEO CERVIX UTERI UNS	8	1	1	2	1	3
UNDER 35	10	2	0	3	-	-	1420 MAL NEO CORPUS UTERI	8	1	2	2	1	3
35-44	214	34	2	31	33	1	1830 MAL NEO OVARY	8	1	3	7	2	4
45-54	274	36	2	32	42	2	1547 MAL NEO OF RECTUM	7	1	1	8	1	2
55-64	155	24	3	22	20	1	1850 MAL NEO HEAD FACE NECK	5	1	1	5	1	1
65+	23	4	1	17	4	1	1703 MALIGN NEO BONES SITE UNS	5	1	21	-	1	3
REGION	638	100	2	100	100	1	2377 NEUROFIBROSITIS	4	1	21	-	0	2
EAST	163	28	2	22	13	1	2019 HODGKINS DISEASE UNSPEC	3	0	1	8	-	-
MIDWEST	121	19	2	23	50	1	1424 MAL NEO VULVA UNSPEC	3	0	3	3	-	-
SOUTH	255	40	2	31	33	2	1853 MAL NEOPLASM DUCTURA	2	0	17	-	-	-
WEST	37	15	1	19	14	2	1851 INTRACRANIAL BILE DUCTS	2	0	7	6	-	-
							2348 NEO UN BEN PLASMA CELLS	2	0	28	1	-	-
							18 SYMPTOMS-ALL DEFINED CON	65	10	0	4	14	14
							7808 CHRONIC PAIN SYNDROME	50	8	4	34	2	10
							7283 UNK-UNSPEC CAUSE OTH	10	1	0	0	0	6
							7840 HEADACH	3	0	0	0	1	-
							7250 ABDOMINAL PAIN	2	0	0	2	1	-
							13 MUSCULOSKELETAL CONNECT TISS	61	9	0	10	5	5
							7245 DISORDERS OF SACRUM	18	3	3	15	-	-
							7225 DIS BONE-CARY OTH-UNSP	11	2	7	7	1	-
							7155 OSTEOPOROSIS UNSPEC	8	1	0	4	2	5
							7245 BACKACHE UNSPEC	7	1	0	7	2	-
							7240 SPINAL STENOSIS NOT CERV	5	1	1	3	1	1
							7222 DISP INTERVERT DISC UNS	4	1	0	4	-	-
							7184 PAIN IN JOINT	4	1	0	4	-	-
							17 INJURY AND POISONING	32	5	0	1	-	-
							8000 FRACTURES	21	3	0	25	1	-
							8300 DISLOCATIONS	4	1	0	4	-	-
							8200 OTH ACCIDENTS-POISONINGS	4	1	0	5	-	-
							8700 LACERATIONS, OPEN WOUNDS	4	1	0	3	-	-
							74 SPEC COND W/O SICKNESS	25	4	0	7	2	2
							8570 POST OP SURGICAL EXAM	25	4	0	48	7	2
							06 DIS OF CNS SENSE ORGS	23	3	0	1	1	3
							3519 HERED-10TH PERIPH NEU UN	11	2	2	7	1	3
							3363 SPINAL CURV-DIS UNSP	6	1	7	0	1	-
							7225 MENINGITIS UNSPECIFIED	2	0	3	15	-	-
							05 DIS OF DIGESTIVE SYSTEM	12	2	6	2	-	-
							5782 OBSTRUCTION OF BILE DUCT	8	1	22	0	-	-
							5808 UNK INTSTINAL OBSTRUCT	3	1	1	0	-	-
							01 INFECTIVE PARASITIC DIS	10	1	0	0	-	-
							0421 HIV-CAUSED SPEC INFECT	7	1	4	2	-	-
							0631 MZ WITH OTH NERV SYST CO	3	0	1	3	-	-
							10 G W DISORDERS	8	1	0	-	-	-
							8190 URINARY BEN TR FIRST FEM	2	1	51	1	-	-
							5897 MENSTRUATION	2	0	0	-	-	-
							ALL OTHERS	17	3	-	3	1	1

DIAGNOSIS VISITS (OOO)	12 MONTHS				CURR QTR	APPEARANCES (OOO)	12 MONTHS				CURR QTR	
	CURRENT		PRIOR				CURRENT		PRIOR			ALL DRUGS
	NO	X	X	Z			NO	Z	Z	X		
CONCOMITANT DRUGS						THERAPY	560	100	100	100	100	
USED ALONE	244	43	38	28	NEW CONTINUED	163	30	23	48	21		
USED WITH	298	57	62	72		392	70	77	51	78		
MORPH/OP, M/INH.	110	18	14	27	VISIT STAGE	539	100	100	100	100		
COBAMINOCOMB, M/INH	85	10	16	8	FIRST	36	6	8	33	2		
CA/TRANSPL, CYTO GTH	40	6	4	15	SUBSEQUENT	557	84	82	87	88		
ANTINAUSEANTS	32	5	3	7	ISSUANCE	585	100	100	100	100		
MIM, TRNQ, BENZOTIAZ	24	4	3	2	RX	370	85	54	53	82		
CORT, PLAIN, ORAL	23	4	4	5	SAMPLE W/RX	-	-	0	3	-		
ANTIARTHRITES, SYST.	20	3	2	2	ADMIN.	-	-	-	3	-		
MIX	22	5	2	5	DISPENSED	-	-	0	8	-		
MORPHINE SULFATE	31	5	5	3	SOLD	-	-	0	1	-		
ROXANOL	31	5	5	12	RECOMMENDED	5	1	2	6	1		
PENCICET	28	5	9	1	WOSP. ORDER	124	22	22	17	20		
BILAUDID	21	3	3	4	NOT ISSUED	86	12	11	15	12		
ELAVIL	11	3	1	5								
VALIUM	15	2	1	-								
RECADRON	14	2	2	2								
MEGACE	13	2	0	4								
COMPAZINE	13	2	2	4								
NAPROSYN	12	2	1	-								
SEMOGOT S	10	2	2	3								
AVERAGE NUMBER OF CONCOMITANT DRUGS = 0.82												
APPEARANCES (OOO)	12 MONTHS				CURR QTR	MENTIONS (OOO)	12 MONTHS				CURR QTR	
	CURRENT		PRIOR				CURRENT		PRIOR			
	NO	X	X	Z			NO	Z	Z	Z		
FORM	836	100	100	100		DESIRED ACTIONS	543	100	100	100		
ORAL SOLID	632	85	100	100	NERVOUS SYSTEM- PAIN	561	89	100	87			
ORAL LIQUID	-	-	-	-	PAIN RELIEF	405	71	75	73			
OPHTHALMIC	-	-	-	-	ANALGESIC	140	25	24	18			
OTIC	-	-	-	-	RESPIRATORY SYSTEM	8	1	-	3			
NASAL	-	-	-	-	INFECTIOUS/PARASITIC DIS	7	0	-	-			
INJECTABLE	-	-	-	-	NEOPLASMS	-	-	0	-			
TOPICAL	-	-	-	-								
RECTAL, SYST	-	-	-	-	NO REASON GIVEN	84	-	-	-	-		
INHALANTS	-	-	-	-								
TRANSDERMAL	-	-	-	-								
ALL OTHERS	4	1	-	-								
APPEARANCES (OOO)	STRENGTH											
	X	Z	X	Z								
PRODUCT STRENGTH BY SIGMA	CURRENT 12 MONTHS											

Attachment 7

RMP 7
Incident Team Schematic

Proposed Response Procedure: Serious Adverse Events Associated
with *Actiq*

Incident Report Received and Logged



Manager: Abbott Medical Communications--Susan Lenarz
Actiq Incident Review Team Alerted

<i>Actiq</i> Incident Review Team:	Director, Medical Affairs	David Mayer, MD
	Director, Regulatory	Dave Guzek
	Business Director	John Heden
	G.M, Alt. Site Sales	Peter Baker
	V.P. Medical Comm (Anesta)	Steve Shoemaker, MD

Action Teams Assembled

Research Team Assigned:

R&D Technical Staff
Medical Staff
Marketing
Manufacturing
Quality Assurance

Investigatory Team Assigned

Immediate Telephone Follow-up
Within 24 hours of receipt
Trained Clinical Assessment Team
Obtain all necessary information
Field investigation as necessary

Review Assessment & Action Plan

Field Response

Technical Review

Close Out and Reporting