FENTORA® (fentanyl buccal tablet) LEARNING SYSTEM

Module 3

Risk Minimization Action Plan

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Supporting references for the text in this module are on file at the Cephalon Sales Training and Development department.

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Introduction

This module reviews the definition of a Risk Minimization Action Plan (RiskMAP) as well as the RiskMAP relevant to *FENTORA*® (fentanyl buccal tablet), which is indicated only for the management of breakthrough pain (BTP) in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

The *FENTORA* RiskMAP is known as the SECURE Program. SECURE stands for Solutions through Education, Communication, and Understanding Risk minimization Excellence. Specific goals and objectives for this program are presented in Section IV of this module.

Learning Objectives

Learning objectives provide a guide for specific and measurable knowledge and understanding that you should have at the conclusion of training. After you finish this module, you will be able to meet the following objectives.

1. Describe the RiskMAP procedure and the reasons for its use.
2. State the three key goals/risks addressed by the *FENTORA* RiskMAP (SECURE Program).
3. Describe the importance of providing those three key goals to each health care professional during each sales call.

Glossary

Abuse: drug abuse (limited to medicinal products only) is defined as "a persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects" (Volume IX of Pharmacovigilance; The Rules of Governing Medicinal Products in the EU).

Diversion: willful transfer of a drug from legitimate supply (manufacture, distribution, or storage in hospitals, pharmacies, or physicians' offices) and/or patients for whom the drug has been prescribed to unauthorized users and/or for illegal sale.

Guillain-Barré [GEE an buh RAY] syndrome: acute polyneuritis (acute inflammatory nerve damage) of unknown cause; can cause paralysis that is temporary or permanent.

Misuse: use of a medication, prescribed by a physician, in a manner which is not prescribed.

Supply chain: begins with Cephalon's receipt of fentanyl citrate for manufacturing and packaging of *FENTORA*® through the receipt of *FENTORA* by the patient.

I. INTRODUCTION TO RISK MANAGEMENT

This section reviews the general characteristics of a RiskMAP.

A. Definition of Risk Management

Concurrent with their benefits, all pharmaceutical products are associated with some risk, whether from unwanted side effects, dependency, and toxicity from **misuse** or overdosage, or from accidental ingestion by someone other than the patient. The Food and Drug Administration (FDA) standard for approval of a pharmaceutical product is whether that product is safe and effective for its labeled indications. "Safe," however, does not mean free from risk in this context; instead, it refers to the probability and clinical significance of beneficial effects relative to the likelihood and severity of undesirable effects, or the benefit-to-risk ratio.

All pharmaceutical products carry some risk associated with their use.

Risk management is the process, in accordance with the FDA governances and guidances, by which benefits are maintained while risks are minimized. This process is iterative and should continue throughout the life of a product. Risk management has four basic steps:

Risk management has four basic steps.

1) Assess the product's benefit-to-risk ratio.

2) Develop and implement tools to minimize risks while preserving benefits.

3) Evaluate the effectiveness of these tools and reassess the benefit-to-risk ratio.

4) Make adjustments, as appropriate, to risk minimization tools to further improve the benefit-to-risk ratio.

B. Risk/Benefit Assessment

Over a product's life, information emerges to help reassess risks and benefits.

Information on risks and benefits associated with a product will continue to emerge and evolve over the life of the product. Risks and benefits are difficult to quantify because they can apply differently to individuals in specific situations. In a risk/benefit assessment, a number of questions must be asked. How severe is the disease being treated? What would be the outcome if the disease were left untreated? How likely is the treatment to be effective, and how effective is it likely to be? What other therapeutic options are available?

Both individual and population risks must be assessed.

Individual patient concerns are also an issue, as are risks and benefits to the population as a whole. Does the patient understand the risks and benefits associated with treatment? What value does he or she place on each risk and benefit? Do benefits to the population outweigh a rare but serious risk (eg, a vaccine that may prevent pandemic influenza but may cause **Guillain-Barré syndrome** in one out of every 1 million vaccine recipients)?

C. Risk Management Planning

Opioid analgesic products have unique risks.

For most products, routine measures are sufficient to minimize risks and preserve benefits. Such routine measures include FDA requirements for product labeling and adverse event monitoring and reporting. For other products—for example, Schedule II controlled substances, known teratogens, or products that require specialized skills or facilities to safely and effectively administer—FDA recommends developing a Risk Minimization Action Plan (RiskMAP), a strategic safety program designed to meet specific goals and objectives in minimizing the known risks of a product while preserving its benefits.

Some products require a RiskMAP in addition to routine monitoring.

A RiskMAP should address how to achieve particular health outcomes in the context of known safety risks. Goals should be stated in absolute terms, for example, "pregnant or lactating women should never take drug X." While ensuring that no pregnant woman

ever receives drug X would be impossible, as a *goal*, it is a statement of an ideal outcome. RiskMAP goals should be translated into pragmatic, specific, and measurable objectives that result in processes or behaviors that lead to achieving the goals. Examples of processes that can minimize safety risks include:

- targeted education to communicate risks and appropriate safety measures to physicians and patients
- processes that encourage reduced-risk prescribing and use
- systems that guide prescribing and dispensing of a product to the population most likely to benefit and to minimize risks

The FDA expects a product's manufacturer to assess the potential risks and determine when developing a RiskMAP is appropriate. However, at any point, the FDA can recommend that a company develop a RiskMAP based on the agency's interpretation of risk.

RiskMAP goals are stated in absolute terms, whereas objectives are pragmatic, specific, and measurable.

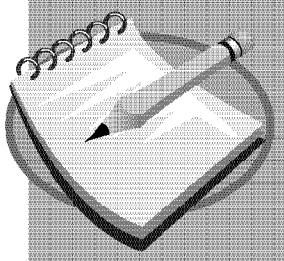
Summary

Risk management refers to the process through which the beneficial effects of a product are maximized, while risks—for example, side effects, toxicity, or accidental ingestion—are minimized. The process involves four basic steps: assessing the benefit-to-risk ratio, developing and implementing the tools to minimize risks while preserving benefits, evaluating effectiveness of those tools, and reassessing the benefit-to-risk ratio and adjusting, as necessary, to further improve that ratio. This process should continue throughout the life of a product.

With any product, information on risks and benefits emerges over the life of the product. A risk/benefit assessment must include data on the severity of the disease being treated and the efficacy of the treatment in question. Individual patient factors must be considered, as must concerns of the population as a whole.

For products such as opioid analgesics, which are associated with special risks, the FDA recommends developing a RiskMAP to meet specific goals (stated in absolute terms) and pragmatic, specific, measurable objectives in risk management. Targeted education programs to address the risk, processes that encourage reduced-risk prescribing, and systems that guide dispensing a product to the most appropriate population are examples of processes that can minimize risks and preserve benefits.

Review Questions (I)



DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. TRUE/FALSE: A Risk Minimization Action Plan is performed prior to product launch to ensure that the benefits of the product are maximized while risks are minimized.

   a. true

   b. false, a Risk Minimization Action Plan is performed for the full 6 months of launch

   c. false, a Risk Minimization Action Plan is performed throughout the life of a product

2. Which of the following would **not** be an element of an effective Risk Minimization Action Plan?

   a. asking the FDA to re-analyze safety data and restrict the recommended patient population

   b. packaging the product in childproof packaging

   c. requiring special certification of pharmacies that dispense the product

   d. targeted physician education on safety risks of a product

Check your responses on page 37.

II. RISK/BENEFIT ASSESSMENT FOR *FENTORA*®

The American Pain Society recommends that patients with chronic pain on a regular opioid treatment should receive supplemental opioids for BTP.

Breakthrough pain (BTP) in patients with cancer is a well-recognized health problem, and it is important that the BTP be managed adequately as part of the overall pain management program. Because of the prevalence and inherent consequences of BTP, the American Pain Society recommends that patients with chronic pain on a regular opioid treatment regimen be provided with supplemental opioid medications for the management of BTP.

Results of a pivotal clinical study demonstrate that *FENTORA* provides analgesia with extensive absorption and a lasting, even improving effect. The efficacy results of that study showed that *FENTORA* had analgesic effects 15 minutes after tablet placement (earliest time point assessed) and maintained superiority in analgesic effect compared with placebo through the 60-minute observation period. Additionally, *FENTORA* demonstrated significant improvement as compared to placebo with regard to all measures of efficacy and at all time points.

FENTORA has been shown to relieve BTP as soon as 10 minutes after administration.

In an efficacy study (Slatkin et al, 2007) conducted subsequent to the initial approval of *FENTORA,* the sum of pain intensity differences (SPIDs) measured at time points from 5 through 60 minutes after study drug administration was significantly greater for BTP episodes treated with *FENTORA* than for episodes for which placebo was given. *[Slatkin, 2007, 4]* In addition, there was a greater reduction in PI at 10 minutes following administration of *FENTORA*, compared with placebo; this difference increased at subsequent time points up to 90 minutes and then was maintained through 2 hours ($p < 0.0001$). *[Slatkin, 2007, 4]*

Fentanyl buccal tablets have unique advantages over ACTIQ (OTFC).

Additional advantages with *FENTORA* are inherent to the buccal tablet formulation. *FENTORA* tablets are uniquely formulated with ingredients and pH adjusters to facilitate absorption of fentanyl through the oral mucosa. This results in a pharmacokinetic profile

which indicates that approximately 50% of the fentanyl in *FENTORA*® is rapidly absorbed and becomes systemically available. These formulation and pharmacokinetic characteristics mean that lower doses of *FENTORA* are needed by patients to attain therapeutically effective plasma concentrations than those required with ACTIQ® (oral transmucosal fentanyl citrate; OTFC), a fentanyl lozenge on a handle. Unlike the active administration of OTFC, administration of *FENTORA* is not only passive but also more discreet and convenient for the patient. This simplicity of administration of a tablet potentially allows for more consistent delivery of fentanyl because it relies on a passive delivery system.

While *FENTORA* has been shown to benefit opioid-tolerant patients with breakthrough cancer pain, the product also has potentially serious side effects and risks. Because *FENTORA* is a potent mu-receptor agonist, there are inherent risks with *FENTORA* to populations for which the product is not intended, particularly those people who are not opioid tolerant. One such risk is respiratory depression. Although respiratory depression was not observed in the *FENTORA* pivotal clinical trial, the potential for this side effect does exist in people who are not opioid tolerant and therefore must be guarded against with interventions beyond routine package labeling.

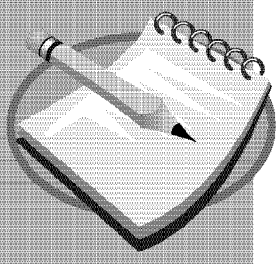
FENTORA can cause respiratory depression, particularly in those who are not opioid tolerant.

Similar to other Schedule II controlled substances, *FENTORA* may be habit forming or potentially abused, and as such, physicians should avoid prescribing it to patients who may **abuse** the product.

Physicians should not prescribe FENTORA to patients who may abuse it.

Lastly, there is also a risk of unintended (accidental) exposure to *FENTORA*. The tablet formulation of *FENTORA* and its packaging is not believed to be intrinsically more interesting or appealing to children than tablet formulations and packaging of other drugs. However, the epidemiology of accidental ingestions indicate that accidental ingestions primarily occur in the pediatric age group, and there is a risk of serious or fatal consequences from accidental exposure to *FENTORA*, particularly in individuals who are not opioid tolerant. Therefore, FENTORA should be stored in a secure place where it is protected from theft and from accidental exposure to children.

The pediatric age group has the highest incidence of accidental ingestions.



Review Questions (II)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. Advantages of *FENTORA*® over OTFC include all of the following, **except**

   a. a more discreet delivery method.
   b. a more effective active ingredient.
   c. less dependence on patient's "active administration."
   d. lower doses needed to control BTP.

2. Risks with *FENTORA*, as with other potent mu-receptor agonists, include all of the following, **except** for

   a. diarrhea.
   b. potential for abuse.
   c. respiratory depression.
   d. unintended (accidental) exposure.

Check your responses on page 37.

III. INTRODUCTION TO THE *FENTORA*® RISKMAP

While all pharmaceutical products have risks, analgesic products—and opioid analgesics in particular—are associated with unique risks in terms of the potential for:

- improper patient selection–
  - the patient must be opioid tolerant
- the potential for misuse, abuse, or **diversion**
- the possibility of accidental ingestion by children

Each of these risks must be carefully assessed and accounted for in developing a risk management plan for a new analgesic product.

In compliance with the FDA's recommendations on risk management planning, Cephalon has developed a RiskMAP for *FENTORA,* the SECURE Program, to address the following major goals and to minimize the following major risks.

A. Used Only by Opioid-tolerant Patients with Cancer

Opioid non-tolerant persons who use opioids risk significant and potentially life-threatening adverse events, including respiratory depression. The risk is present with any dose of an opioid and increases with increasing doses. Patients who are considered opioid tolerant are those who, for ≥1 week, have been taking ≥60 mg/day oral morphine, ≥25 µg/hour transdermal fentanyl, ≥30 mg/day oxycodone, ≥8 mg/day oral hydromorphone, or an equianalgesic dose of another opioid.

Specific guidelines exist for defining patients who are opioid tolerant.

Diversion of opioid products can occur under a variety of circumstances.

B. Misuse, Abuse, or Diversion

The likelihood that an opioid product will be abused is influenced by multiple factors (eg, social, environmental, genetic). Diversion is also known to be an issue with opioid products. Although exact rates of diversion are not known, multiple routes of diversion exist. Diversion may occur through pharmacy theft or fraudulent prescriptions. Persons may attempt to procure opioids from physicians under false pretenses, or persons with legitimate prescriptions may sell their medications.

C. Unintended (Accidental) Exposure to *FENTORA*®

The RiskMAP for FENTORA addresses the risk of accidental ingestion.

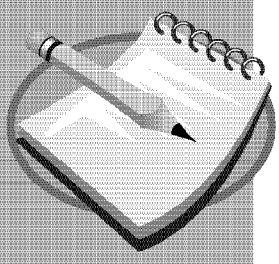
The risk of serious consequences from accidental exposure to *FENTORA* is greater in individuals non-tolerant to opioids. Therefore, the risk of unintended exposure to the drug can be viewed as a component of the first goal described above (used only by opioid-tolerant individuals). And while the tablet formulation and packaging of *FENTORA* are not believed to be intrinsically more interesting or appealing to children than tablet formulations in blister packs of other drugs, the epidemiology of accidental ingestions (which occur primarily in the pediatric age group) and the risk of serious consequences from accidental exposure to *FENTORA* make the risk of unintended exposure to the product one that should be addressed in the *FENTORA* RiskMAP.

Summary

Opioid analgesics are associated with risks that may not be relevant for other pharmaceutical products. In developing the *FENTORA*® RiskMAP (SECURE Program), Cephalon has incorporated goals that address the risks associated with opioid treatment. Patients must be selected carefully on the basis of prior exposure to opioids; persons who are not tolerant to opioids risk life-threatening adverse events. Potential also exists for *FENTORA*, as with other opioids, to be misused by patients or diverted from their intended use and abused recreationally. Diversion can occur during the manufacturing process or distribution or as a result of pharmacy theft, fraudulent prescriptions, or patients selling or giving away their medications. Another significant risk associated with opioids is the possibility that children, who are at higher risk for serious adverse events, may accidentally ingest them.

Therefore, the *FENTORA* RiskMAP addresses the following goals/risks:

- Used only by opioid-tolerant patients with cancer
- Misuse, abuse, or diversion
- Unintended (accidental) exposure to *FENTORA*



Review Questions (III)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. TRUE/FALSE: A patient would be considered opioid tolerant if she had been taking ≥30 mg/day of oxycodone for at least a week.

   a. true
   b. false, the dose would be ≥60 mg oxycodone
   c. false, the dose would have to be taken for at least 2 weeks

2. The RiskMAP for *FENTORA*® addresses unintended (accidental) exposure, in part because accidental ingestions are most common among

   a. blind patients.
   b. elderly adults.
   c. patients with chronic pain.
   d. pediatric individuals.

Check your responses on page 37.

IV. GOALS AND OBJECTIVES OF THE *FENTORA*® RISKMAP

The *FENTORA* RiskMAP (SECURE Program) consists of three clear, absolute goals; each goal is associated with multiple practical, measurable objectives.

Goal 1: *FENTORA* should be used *only* by opioid-tolerant patients with cancer.

Objectives:

i: Educate physicians that *FENTORA* should not be used in opioid non-tolerant patients.

ii: Educate patients that *FENTORA* should be used only by individuals with cancer who are opioid tolerant.

iii: Educate pharmacists and other health care personnel of the importance of *FENTORA* being prescribed, distributed, and used only by opioid-tolerant patients with cancer.

Goal 2: Abuse, misuse, and diversion of *FENTORA* should *not* occur.

Objectives:

i: Ensure adequate controls are instituted and maintained to prevent the diversion of *FENTORA* from Cephalon's **supply chain**.

ii: Ensure adequate education, surveillance, and interventions are instituted and maintained to minimize diversion of *FENTORA* when the product is no longer within Cephalon's supply chain.

iii: Reduce the potential abuse, misuse, and diversion of *FENTORA* by (a) providing education to health care personnel and to pertinent nationwide demographic communities; (b) performing ongoing

surveillance of and reaction to geographical outbreaks of abuse, misuse, and diversion; and (c) cooperating with and providing assistance to law enforcement in investigations of incidents of abuse or diversion.

Goal 3: Unintended (accidental) exposure to *FENTORA*® should *not* occur.

Objectives:

i: Reduce or eliminate accidental exposure through product packaging.

ii: Reduce or eliminate accidental exposure by properly educating patients about "safe product use."

iii: Reduce or eliminate departures from "safe product use" at the time of actual or intended use of *FENTORA*.

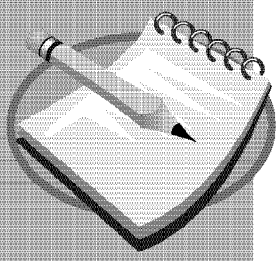
iv: Reduce or eliminate accidental exposure by educating patients to properly store *FENTORA* out of the reach of children and ensure that mechanisms exist to facilitate the prompt return and/or disposal of all unused *FENTORA* when it is no longer needed.

Summary

The *FENTORA*® RiskMAP (SECURE Program) contains three goals, each of which is associated with multiple objectives. First, *FENTORA* should be used *only* by opioid-tolerant patients with cancer. To this end, Cephalon will educate physicians, nurses, pharmacists, and other health care personnel that *FENTORA* should be used only by opioid-tolerant patients with cancer. Cephalon will take steps to ensure that patients are aware that *FENTORA* should be used only by opioid-tolerant patients with cancer.

Second, abuse, misuse, and diversion of *FENTORA* should *not* occur. Consequently, Cephalon has instituted and maintains adequate controls to prevent diversion from the supply chain through to receipt of *FENTORA* by the patient. To minimize diversion when the product is no longer within the supply chain, Cephalon has instituted educational programs for health care personnel and targeted communities, surveillance, and other interventions. Cephalon also cooperates with and provides assistance to law enforcement agencies investigating cases of diversion or abuse of *FENTORA*.

Third, unintended exposure to *FENTORA* should *not* occur. To meet this goal, Cephalon has designed and tested product packaging to reduce unintended access. Cephalon has educated consumers about safe product use both at the point of prescribing and dispensing; Cephalon has aimed to reduce departures from safe use at the point of administration. Finally, Cephalon has taken steps to reduce accidental exposure of *FENTORA* to children and instituted mechanisms to facilitate return and disposal of unused product when it is no longer needed.



Review Questions (IV)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. Because *FENTORA*® should be used *only* by opioid-tolerant patients with cancer, Cephalon

   a. educates health care personnel that *FENTORA* should be used only in opioid-tolerant patients with cancer.

   b. educates pharmacists and nurses on *FENTORA* features and benefits.

   c. monitors the supply chain, from manufacture to distribution.

   d. promotes *FENTORA* only in areas where opioid tolerance is known to be high.

2. Which of the following represents the area over which Cephalon can exert the *greatest* degree of control in preventing diversion?

   a. conducting educational programs in targeted demographic communities

   b. educating health care personnel about potential for abuse

   c. performing ongoing surveillance of abuse

   d. preventing diversion from the supply chain

3. Which of the following is **not** an example of an intervention designed to eliminate unintended exposure to *FENTORA*®?

   a. dispensing product only in childproof packaging

   b. disseminating material that summarizes clinical trial results to prescribers

   c. patient education by physician on good storage practices

   d. providing a toll-free number for product disposal when it is no longer needed

Check your responses on page 37.

V. STRATEGIES AND TOOLS USED TO ACHIEVE THE *FENTORA*® RISKMAP

Health care professionals and patients are given several key messages about FENTORA.

Several key messages are provided to health care professionals and patients in the tools that make up the *FENTORA* RiskMAP (SECURE Program). They convey that *FENTORA*:

- contains fentanyl citrate, a potent Schedule II opioid
- should be used only by opioid-tolerant patients (defined by the package insert) with cancer because of the risk of serious outcomes such as respiratory depression
- has a risk of misuse, abuse, and diversion
- should be kept out of the reach of children
- is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
- is contraindicated in acute pain or postoperative pain

A principal goal of the RiskMAP is to ensure that physicians, pharmacists, and patients are aware and knowledgeable of each of these messages and their implications.

A. Product-specific Safety Features

The FENTORA carton label contains clear warnings for use.

The *FENTORA* carton label clearly notes that *FENTORA* is to be kept out of the reach of children and that *FENTORA* contains medication that could be harmful to someone for whom it has not been prescribed. Labeling also contains information designed to decrease misuse of the product, as well as a warning label on product cartons. The CII status is featured prominently on the label to remind practitioners that *FENTORA* is a controlled substance and has a high potential for abuse.

The carton label advises the patient or caregiver to read the enclosed Medication Guide for important warnings and directions. In addition, the label includes a checklist to remind the pharmacist to encourage the patient to read the Medication Guide. The Medication Guide contains information intended to decrease the risk of accidental exposure to *FENTORA*®. It warns that *FENTORA* should be stored in a secure place, away from children, and that accidental ingestion by a child could result in death. In the event of accidental exposure, the Medication Guide includes instructions to call 911 or go to the nearest emergency room right away.

The carton label also advises the patient to read the Medication Guide, which contains important information.

The tablet formulation and packaging of *FENTORA* is not believed to be intrinsically more interesting or appealing to children than any other tablet in blister packaging. Because of the risk of serious side effects should anyone accidentally ingest *FENTORA*, Cephalon has designed the packaging of *FENTORA* to minimize unintended or accidental exposure. The *FENTORA* double-foil blister pack meets F1 requirements and has passed tests for child resistance and senior friendliness. In addition, the tablets are not visible through the packaging. The blister label warns that *FENTORA* should be kept out of the reach of children and that *FENTORA* should be used immediately upon opening. The dome side of the blister label contains the warning "Only for patients already taking opioids."

FENTORA packaging has been designed to minimize unintended or accidental exposure to the product.

B. Comprehensive Education and Outreach Programs

Cephalon has established a number of specific education and outreach programs for *FENTORA*.

1. Health Care Professional Letters. Health care professionals have been alerted to the risks of *FENTORA* through an introductory letter disseminated at product launch to 10,000 physicians likely to prescribe *FENTORA*, 3,000 pharmacists likely to stock *FENTORA*, and the top 25 Pain Centers of Excellence. The letter emphasized that *FENTORA* should be used only by opioid-tolerant patients with

An introductory letter to health care professionals emphasized proper use.

cancer and informed health care professionals of the potentially life-threatening consequences of accidental use of *FENTORA*® by children or adults. The letter also reinforced the potential for misuse, abuse, and diversion of *FENTORA*.

Cephalon field representatives receive comprehensive RiskMAP training.

2. RiskMAP Training Programs. Cephalon field representatives receive product-specific training that covers the approved prescribing information for *FENTORA*, including the *FENTORA* RiskMAP, risks of using *FENTORA* in opioid non-tolerant persons, and potential for abuse or diversion. Representatives are tested on the training and are required to verify their understanding of the information in the *FENTORA* RiskMAP. In addition, identified physicians trained on *FENTORA* clinical information are trained on the *FENTORA* RiskMAP.

CME/CE units on prescription drug misuse, abuse, and diversion are offered to health care professionals.

3. CMEs and CEs for Health Care Professionals. Cephalon supports independent continuing medical education on prescription drug misuse, abuse, and diversion targeted to physicians likely to prescribe *FENTORA*. Cephalon contacted the top 25 Pain Centers of Excellence and various professional societies to offer additional educational opportunities to learn about *FENTORA*, including the risk of use in opioid non-tolerant persons, potential for abuse and diversion, and other key messages from the *FENTORA* RiskMAP.

The Medication Guide emphasizes the need for the patient to be opioid tolerant, and the serious consequences of inappropriate use.

4. Medication Guide. The carton label directs patients to read the enclosed Medication Guide, an FDA-approved piece of labeling that must be distributed with each prescription. It also includes a reminder to the pharmacist to instruct the patient to read the Medication Guide. The *FENTORA* Medication Guide emphasizes, in understandable, nontechnical language, the need for the patient to be opioid tolerant. It warns of the serious consequences—including death—that can occur if *FENTORA* is used by an opioid non-tolerant person.

The Medication Guide also provides information intended to minimize misuse, abuse, and diversion. For example, it includes a section titled "How should I use *FENTORA*®?" that provides instructions on proper administration. It warns that patients may become physically dependent on or addicted to *FENTORA*. To discourage diversion, it warns that selling or giving away *FENTORA* is against the law and cautions patients to store *FENTORA* in a secure place to prevent it from being stolen.

The Medication Guide also reviews how to appropriately use the product.

The Medication Guide is included in all *FENTORA* packaging and is available to prescribers and pharmacies that stock *FENTORA* via an 800 number, the product website, and Cephalon field representatives. Patients also benefit from the use of written counseling aids provided by Cephalon to physicians and pharmacists. These aids encourage an open dialogue about *FENTORA* between the health care professional and the patient, thereby encouraging active participation of the patient in his/her medical care.

Physicians and pharmacists receive written counseling aids.

C. Guidance on Prescribing, Dispensing, and Use of Schedule II Controlled Substances (CII)

FENTORA is classified as a Schedule II controlled substance by the Drug Enforcement Agency (DEA), and this is one of the primary tools that helps limit the degree to which it is abused and diverted. Federal and state regulations govern the manufacturing, distribution, prescribing, dispensing, storage, and disposal of CII products, and extensive controls, record-keeping requirements, and auditing functions are in place to limit the risk of abuse and diversion. Prescriptions for CII products must be handwritten in ink or typed and signed by the practitioner. In some states, verbal prescriptions are allowed in a genuine emergency, and they must be confirmed in writing within 72 hours. (Note: state regulations and confirmation times may vary.)

Prescriptions for CII products must follow specific rules.

Cephalon applies controls at every point from receipt of fentanyl citrate to shipment to wholesalers.

In evaluating the tools to reduce the risk of misuse, abuse, and diversion associated with the use of *FENTORA*®, Cephalon identified several points of intervention in the product's safe-use pathway. The early part of this supply chain is most directly under Cephalon's control because of the company's internal standard operating procedures and auditing capabilities. Controls are applied from the time Cephalon is in receipt of fentanyl citrate throughout the manufacturing and packaging of the finished product and through distribution to wholesalers. To help minimize the risk of diversion of *FENTORA*, Cephalon tracks every shipment of *FENTORA* from its manufacturing sites to its receipt at the wholesaler. Drug accountability is maintained to ensure diversion has not occurred from the time the product departs from Cephalon to when it is received by the wholesaler. Wholesalers who purchase product from Cephalon are alerted to the goals of the *FENTORA* RiskMAP, and the wholesalers verify that they have processes and procedures in place to minimize the risk of diversion when the product is received by the pharmacies. Pharmacies are responsible and held accountable for minimizing the risk associated with diversion at the point of dispensing.

Physicians should use caution in identifying appropriate candidates for therapy with FENTORA.

At the point of prescribing, physicians should use caution when prescribing *FENTORA* to patients and should be aware of circumstances, symptoms, and signs that could contribute to an individual's risk of abuse. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction before being prescribed *FENTORA*. All patients receiving *FENTORA* should be routinely monitored for signs of misuse, abuse, and addiction. Physicians should also be familiar with methods used by individuals to obtain Schedule II opiates illicitly (eg, doctor shopping, feigning illness or pain). Physicians who prescribe *FENTORA* should balance the risks of product misuse, abuse, and diversion with the medical need to adequately treat pain.

Similarly, pharmacists should also exercise caution when dispensing *FENTORA*® to patients. Pharmacists, too, should have familiarity with factors that could contribute to an individual's risk of abuse and should be knowledgeable about methods used by individuals to obtain Schedule II opiates illicitly (eg, fraudulent prescriptions, pharmacy theft).

Appropriate caution is also needed when pharmacists dispense FENTORA.

FENTORA is a federally controlled substance (CII), because it is a strong opioid pain medication that can be abused by people who abuse prescription medications or street drugs. Patients should be counseled that their risk for abuse and addiction may be higher if they have a history of abuse of other medications, street drugs, or alcohol or if they have a history of mental illness. Patients should also be counseled that *FENTORA* contains a federally controlled substance and that to sell or give their medication to others is a violation of the law. Patients should also be advised that they could become targets for those who abuse prescription medications or street drugs, and that they should always store *FENTORA* in a secure place.

Patients should receive counseling about the risks and benefits of therapy with FENTORA.

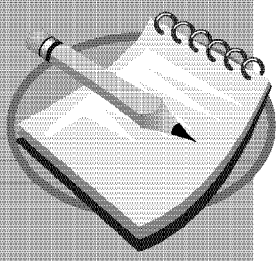
Summary

A number of tools make up the *FENTORA*® RiskMAP (SECURE Program). These are designed to minimize the potential risks associated with the product while preserving benefits. On the product level, the *FENTORA* package insert contains a boxed warning about the risk of use in opioid non-tolerant persons and information about potential abuse and diversion. The *FENTORA* carton is clearly labeled with information designed to convey its risks and decrease misuse of the product. The carton includes a Medication Guide for patients and caregivers; it contains understandable, nontechnical information on correct use, secure storage, potential for abuse and diversion, and instructions to call 911 for emergency help in the event of accidental ingestion. The *FENTORA* blister pack meets the highest federal standards for child safety and is intended to mitigate the risk of accidental ingestion by children.

Comprehensive education and outreach programs are conducted to increase the safe use of *FENTORA*. At launch, an introductory letter was sent to physicians, pharmacists, and the top 25 Pain Centers of Excellence. Health care professionals also have the opportunity to earn CE and CME credits by attending educational sessions on risks associated with *FENTORA*. Cephalon field representatives receive product-specific training on the safe use of *FENTORA*.

Because *FENTORA* is a CII drug, federal and state regulations govern its distribution, prescribing, storage, and disposal to limit abuse and diversion. CII controlled substances may be prescribed only according to specific procedures. Physicians should use caution when prescribing *FENTORA* and be aware of signs that could indicate a patient at high risk for abuse. Similarly, pharmacists should be familiar with factors that contribute to the risk of abuse and be aware of methods used to illicitly obtain drugs. Patients with a history of drug abuse or

alcoholism should be counseled that they are at higher risk for abusing *FENTORA*®. Patients should also be counseled to store their medications in a secure place out of the reach of children to prevent accidental exposure. Patients should also be counseled that they may become targets for people who abuse prescription medications.



Review Questions (V)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. TRUE/FALSE: The dome side of the *FENTORA*® blister pack is printed with the words "For Buccal Administration."

   a. true

   b. false, the blister pack says "Do Not Swallow."

   c. false, the blister pack says "Only for patients already taking opioids."

2. Which of the following is **not** an educational intervention described in the *FENTORA* RiskMAP?

   a. annual "risk summit" meeting of Pain Centers of Excellence

   b. CME/CEs for health professionals

   c. letter to health care practitioners

   d. RiskMAP field representative training

3. The *FENTORA* Medication Guide is a patient-friendly text included in each carton of *FENTORA*. It contains information on

   a. proper storage of *FENTORA*.

   b. sharing or selling *FENTORA*.

   c. risk of serious consequences if *FENTORA* is used by an opioid non-tolerant person.

   d. all of the above

4. Which of the following does **not** indicate a patient at risk for abusing opioids?

   a. family history of alcoholism

   b. history of chronic pain

   c. history of presenting to multiple doctors with complaints of nonspecific pain

   d. severe clinical depression

Check your responses on page 37.

VI. EVALUATION OF THE *FENTORA*® RISKMAP

The FENTORA RiskMAP includes methods for evaluation and surveillance.

As noted, risk management is an iterative process that should continue throughout the life of a product. In the absence of a feedback loop, the efficacy of risk management is diminished. As a result, the *FENTORA* RiskMAP contains provisions for ongoing evaluation and surveillance, results of which are used to refine the risk management process.

Present the key goals in every conversation with health care providers.

Your role in the *FENTORA* RiskMAP (SECURE Program) is to be sure that you clearly present the key goals of the program, utilizing the RiskMAP flashcard educational piece, in *every* conversation with the health care provider.

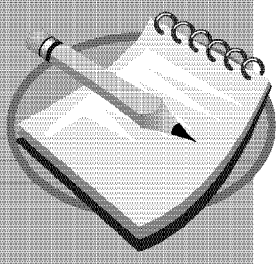
Evaluations are scheduled.

The *FENTORA* RiskMAP continues to be evaluated and, if necessary, modified, through a variety of methods. These include surveillance of adverse events and claims data, and surveys of prescribers, pharmacists, and patients. The evaluations are conducted on a scheduled basis and progress in this area and any resulting changes in the RiskMAP will be submitted to the FDA.

Summary

Because a Risk Minimization Action Plan is an iterative process, the tools identified in the *FENTORA*® RiskMAP are evaluated on an ongoing basis, and results are used to refine and improve the process of risk management. A number of surveillance and monitoring strategies are used at the prescriber, pharmacist, and patient levels to assess the effectiveness of educational interventions and other risk management tools.

Your role in the *FENTORA* RiskMAP (SECURE Program) is to be sure that you clearly present the key goals/risks of the program, utilizing the RiskMAP flashcard educational piece, in *every* conversation with the health care provider.



Review Questions (VI)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. The rationale for ongoing evaluation of the *FENTORA*® RiskMAP is that it

   a. aids the development of safer drugs in the future.

   b. is required by the FDA.

   c. provides feedback to further improve risk management.

   d. all of the above

2. Your role in the *FENTORA* RiskMAP is to

   a. describe clearly to physicians how they will be surveyed.

   b. participate in planning changes to the RiskMAP based on survey feedback.

   c. use the RiskMAP flashcard education piece to clearly present the key goals of the program in every conversation with health care providers.

   d. all of the above

Check your responses on page 37.

Integrative Summary

All pharmaceutical products are associated with risk from side effects, dependency, toxicity, or accidental ingestion. Risk management is a necessary process to minimize these risks while preserving a product's benefits. Opioid analgesics, in particular, are associated with dangerous and sometimes life-threatening risks. Patients who are not tolerant to opioids risk respiratory depression. Opioids have a high potential for abuse and diversion. Opioids may be particularly dangerous if they are ingested by someone other than the intended patient, such as a child.

A RiskMAP should consist of clear, absolute risk management goals, each of which is associated with practical, achievable, measurable objectives. For *FENTORA*®, goal 1 is that it should be used *only* by opioid-tolerant patients with cancer. Goal 2 states that abuse, misuse, and diversion of *FENTORA* should *not* occur. Goal 3 states that unintended or accidental exposure to *FENTORA* should *not* occur. In the *FENTORA* RiskMAP, each of these goals is associated with multiple objectives.

The *FENTORA* RiskMAP (SECURE Program) describes numerous features and programs that are designed to meet the risk management goals and objectives. The product packaging itself is designed to alert health care professionals and patients to the risks and indications of *FENTORA*, and it meets F1 requirements for child resistance. A Medication Guide is included to emphasize the need to be opioid tolerant and warn of the consequences of accidental ingestion. Comprehensive training programs are addressed to health care professionals on the indication, risk, and implications of diversion for *FENTORA*. Cephalon field representatives also receive comprehensive training on risk management.

Because *FENTORA*® is a CII controlled substance, it is subject to federal and state regulations to limit the risk of abuse and diversion. The early part of the product supply chain—from manufacture to distribution to wholesalers—is directly under Cephalon's control, and measures are in place during this process to minimize risk of diversion. Wholesalers are alerted to the goals of the *FENTORA* RiskMAP and must verify that they have procedures in place to minimize the risk of diversion. Physicians and pharmacists are alerted to the risk of diversion, methods commonly used to obtain Schedule II drugs illegally, and signs that may indicate an individual at risk for abuse. Patients are educated on the risk of abuse and the legal ramifications of diversion.

Cephalon monitors the effectiveness of the *FENTORA* RiskMAP on an ongoing basis, and results of monitoring inform changes to the RiskMAP. Through the iterative process of risk management, Cephalon is able to minimize the risks associated with *FENTORA* while retaining its benefits in treating breakthrough cancer pain.

Your role in the *FENTORA* RiskMAP is to be sure that you clearly present the key goals/risks of the program, utilizing the RiskMAP flashcard educational piece, in *every* conversation with the health care provider.

Answers to Review Questions

I. 1. c
2. a

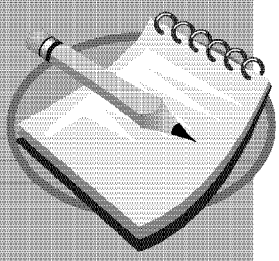
II. 1. b
2. a

III. 1. a
2. d

IV. 1. a
2. d
3. b

V. 1. c
2. a
3. d
4. b

VI. 1. c
2. c



Self-assessment Post-test

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. Which of the following is **not** one of the four basic steps in risk management?

   a. assess the product's risk-to-benefit ratio
   b. develop tools to minimize risks
   c. make adjustments to risk minimization tools
   d. report findings to health care professionals

2. Why is a Risk Minimization Action Plan particularly important for opioid analgesics?

   a. Opioid analgesics are associated with a high potential for misuse, abuse, or diversion.

   b. Opioids are appealing to children.

   c. Opioids have similar effects on all persons.

   d. Prescriptions for opioids are easily obtained.

3. Which of the following is the *best* example of a RiskMAP goal?

   a. Drug X has *never* been studied in pediatric populations.

   b. Drug X should never be given to patients with hepatic impairment.

   c. Patients on drug X *must* be aware of the risk for night blindness.

   d. Women who become pregnant should discontinue drug X *as soon as possible*.

4. Which of the following would address Goal 2: Abuse, misuse, and diversion of *FENTORA*® should **not** occur?

   a. educate patients that only opioid-tolerant patients with cancer should use the product

   b. improve child-resistant packaging

   c. perform ongoing surveillance to monitor for abuse, misuse, and diversion

   d. urge physicians to have their patients minimize use of *FENTORA*

5. The *FENTORA* carton label includes a reminder to the pharmacist that

   a. dispensing *FENTORA* without a prescription is unlawful.

   b. fentanyl, like all opioids, is associated with risk for abuse and diversion.

   c. he or she should instruct the patient to read the Medication Guide.

   d. patients under the age of 10 should *never* be given *FENTORA*.

6. How does Cephalon minimize risk of diversion at the point of the wholesaler?

   a. distributing product only to FDA-approved wholesalers

   b. educating wholesalers about the dangers of abuse and diversion

   c. radiolabeling product so that it can be tracked by GPS

   d. requiring wholesalers to have processes in place that minimize diversion risk

7. TRUE/FALSE: Patients who exhibit signs that they are at risk for abuse should **not** be given *FENTORA®*.

   a. true

   b. false, a psychiatrist should make the final determination whether *FENTORA* is needed

   c. false, physicians should balance the risk of abuse with the need to treat pain

Check your responses on page 42.

Answers to Self-assessment Post-test

1. d (page 5, paragraph 3, numbers 1, 2, 4)
2. a (page 13, paragraph 1, bullet 2)
3. b (page 6, paragraph 4)
4. c (page 17, paragraph 7; page 18, paragraph 1)
5. c (page 23, paragraph 1)
6. d (page 26, paragraph 1)
7. c (page 26, paragraph 2)