

media fact sheet

ACTIQ® (ORAL TRANSMUCOSAL FENTANYL CITRATE) [C-II] AND FENTORA® (FENTANYL BUCCAL TABLET) [C-II] RISK EVALUATION AND MITIGATION STRATEGY (REMS)

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| What are the goals of the REMS? | The goals of the REMS are to ensure proper patient selection, to prevent accidental exposure and inappropriate conversion between fentanyl products, as well as to mitigate the potential risks of misuse, abuse, addiction, and overdose. |
| What is the REMS? | <p>The ACTIQ and FENTORA REMS integrates available technology to help assure appropriate patient selection and education, checks and balances within the distribution channel, and dispensing of the medication for the appropriate, intended use.</p> <ul style="list-style-type: none">– Ensures appropriate patients have access to their medicines while preserving availability at retail pharmacy– Enrolls prescribers and pharmacies through education on appropriate patient selection and additional key safety information in order for patients to receive the medications they need– Enhances the dialogue around patient safety at point of prescribing through required patient education about safe and appropriate use– Utilizes existing and familiar technology within the normal stakeholder workflow in order to minimize disruption |
| How is REMS information stored? | A central database captures and accesses data from all stakeholders in a HIPAA-compliant manner. The central database will track all enrolled distributors, prescribers, pharmacies and patients and serve as a checkpoint to confirm that patients have been educated about safe use of ACTIQ or FENTORA. |
| Who is required to enroll in the REMS? | Wholesalers, pharmacies and healthcare professionals who distribute, dispense and prescribe ACTIQ or FENTORA must enroll in the system. Healthcare professionals who prescribe these products will also educate patients as part of the program and this must be documented. |
| What are the responsibilities of each of the key stakeholders in the REMS? | <p>Under this REMS, pharmacies and healthcare professionals who dispense and prescribe ACTIQ or FENTORA will enroll by completing an education module and knowledge assessment focused on safety information including appropriate patient selection. Healthcare professionals who prescribe these products will also educate patients as part of the program and this must be documented using a Patient-Prescriber Agreement (PPA). The PPA needs to be submitted to the REMS program by the HCP in order to enroll the patient.</p> <p>Wholesalers will be enrolled and must verify pharmacy enrollment before they can distribute ACTIQ and/or FENTORA to any pharmacy.</p> |

What is the role of the patient in the REMS? In order to write a prescription for ACTIQ or *FENTORA*, the healthcare professional will first confirm that the patient is opioid-tolerant. Healthcare professionals who prescribe these products will educate the patient with safety messages about ACTIQ or *FENTORA* with a Medication Guide, and patients will need to review and sign a Prescriber-Patient Agreement.

Patients will then go to an enrolled pharmacy to fill their prescription.

What is a REMS? A REMS – Risk Evaluation and Mitigation Strategy – is a product- or class-specific risk management program approved by FDA. This FDA requirement is being applied to many products based on a new law passed by Congress in 2007 that gives the agency more authority to enforce efforts to minimize risks associated with a specific medication or biologic. For more information about REMS, please visit the FDA website: www.fda.gov.

Important Safety Information

WARNING: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with ACTIQ have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid for a week or longer.

ACTIQ is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

ACTIQ is contraindicated in the management of acute or postoperative pain including headache/migraine.

When prescribing, do not convert patients on a mcg per mcg basis to ACTIQ from other fentanyl products.

When dispensing, do not substitute an ACTIQ prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of ACTIQ compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ACTIQ for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ACTIQ. If the breakthrough pain episode is not relieved 15 minutes after completion of the ACTIQ unit, patients may take ONLY ONE additional dose using the same strength and then must wait at least 4 hours before taking another dose [see *Dosage and Administration (2.2)*].

ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ACTIQ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ACTIQ in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ. All units must be kept out of the reach of children and opened units properly discarded [see *Warnings and Precautions (5.3)*, *Patient Counseling Information (17.5, 17.6)*, and *How Supplied/Storage and Handling (16.2)*].

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

The concomitant use of ACTIQ with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see *Drug Interactions (7)*].

Because of the risk for misuse, abuse, addiction, and overdose, ACTIQ is available only through a restricted distribution program, required by the Food and Drug Administration, called the ACTIQ REMS Program (Risk Evaluation and Mitigation Strategy). Under the ACTIQ REMS Program, healthcare professionals (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute ACTIQ, respectively. [See *Warnings and Precautions (5.10)*] Further information is available at www.actiqandfentorarems.com or by calling 1-888-688-6885.

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

Reports of serious adverse events, including deaths in patients treated with FENTORA have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

FENTORA is indicated only for the management of breakthrough pain in adult patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine. FENTORA is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure to opioids.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA. Carefully consult the Initial Dosing Recommendations table. [See Dosage and Administration (2.1)]

When dispensing, do not substitute a FENTORA prescription for other fentanyl products. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. [See Dosage and Administration (2.1)]

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all tablets out of the reach of children. [See Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

The concomitant use of FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression [see Drug Interactions (7)].

Because of the risk for misuse, abuse, addiction, and overdose, FENTORA is available only through a restricted distribution program, required by the Food and Drug Administration, called the FENTORA REMS Program (Risk Evaluation and Mitigation Strategy). Under the FENTORA REMS Program, healthcare professional (who prescribe to outpatients), as well as outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense, and distribute FENTORA, respectively. [See Warnings and Precautions (5.1)] Further information is available at www.actiqandfentorarems.com or by calling 1-888-688-6885.

Contraindications:

- ACTIQ and FENTORA must not be used in opioid non-tolerant patients because life-threatening respiratory depression and death can occur at any dose in opioid non-tolerant patients
- ACTIQ and FENTORA are contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain
- ACTIQ and FENTORA are contraindicated in patients with known hypersensitivity to any of the components or the drug fentanyl

Warnings and Precautions:

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted
- Titrate ACTIQ and FENTORA cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression
- Administer ACTIQ and FENTORA with extreme caution in patients susceptible to intracranial effects of CO₂ retention

- Application site reactions occurred in 10% of patients in *FENTORA* clinical trials and ranged from paresthesia to ulceration and bleeding
- Full and partially consumed ACTIQ units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available (ACTIQ Child Safety Kit)

Adverse Reactions:

- For ACTIQ, most common adverse reactions during titration phase (frequency $\geq 5\%$): nausea, dizziness, somnolence, vomiting, asthenia, and headache. Most common adverse reactions during longer-term treatment (frequency $\geq 5\%$): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia.
- For *FENTORA*, most common adverse reactions during titration phase (frequency $\geq 10\%$): nausea and dizziness. Most common adverse reactions during longer-term treatment (frequency $\geq 10\%$): nausea, vomiting, fatigue, anemia, dizziness, peripheral edema, constipation, asthenia, dehydration, and headache

Drug Interactions:

- Monitor patients who begin therapy with, or increase dose of, inhibitors of CYP 3A4 for signs of opioid toxicity
- Monitor patients who stop therapy with, or decrease dose of, inducers of CYP 3A4 for signs of opioid toxicity

Use in Specific Populations:

- Administer ACTIQ and *FENTORA* with caution to patients with severe hepatic or renal disease.

Please see full prescribing information, including boxed warning, at www.actiq.com and www.fentora.com.

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