FENTANYL CITRATE- fentanyl citrate lozenge
SpecGx LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORAL TRANSMUCOSAL FENTANYL CITRATE safely and effectively. See full prescribing information for ORAL TRANSMUCOSAL FENTANYL CITRATE.

ORAL TRANSMUCOSAL FENTANYL CITRATE, oral transmucosal lozenge, CII

Initial U.S. Approval: 1968

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, oral transmucosal fentanyl citrate is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (5.1)**
- **Accidental ingestion of oral transmucosal fentanyl citrate, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (2.8, 5.2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to oral transmucosal fentanyl citrate. (5.5)**
- **When dispensing, do not substitute with any other fentanyl products. (5.5)**
- **Oral transmucosal fentanyl citrate exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.6)**
- **Oral transmucosal fentanyl citrate is available only through a restricted program called the TIRF REMS. Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients are required to enroll in the program. Patients must be opioid tolerant to receive a TIRF medicine. (5.7)**
- **Prolonged use of oral transmucosal fentanyl citrate during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

INDICATIONS AND USAGE

Oral transmucosal fentanyl citrate is an opioid agonist indicated for the management of breakthrough pain in cancer patients 16 years of age and older 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, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of

another opioid. Patients must remain on around-the-clock opioids while taking oral transmucosal fentanyl citrate.

Limitations of Use

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine or dental pain. (4)
- As a part of the TIRF REMS, oral transmucosal fentanyl citrate may be dispensed by outpatient pharmacies only to outpatients enrolled in the program. (5.7) For inpatient administration of oral transmucosal fentanyl citrate, patient and prescriber enrollment are not required.

DOSAGE AND ADMINISTRATION

- Patients must require and use around-the-clock opioids when taking oral transmucosal fentanyl citrate. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with oral transmucosal fentanyl citrate. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.1, 5.4, 5.6)
- Initial dose of oral transmucosal fentanyl citrate: 200 mcg. Prescribe an initial supply of six 200 mcg oral transmucosal fentanyl citrate units. (2.3)
- Individually titrate to a tolerable dose that provides adequate analgesia using single oral transmucosal fentanyl citrate dosage unit per breakthrough cancer pain episode. (2.4)
- No more than two doses can be taken per breakthrough pain episode. (2.4, 2.5)
- Wait at least 4 hours before treating another episode of breakthrough pain with oral transmucosal fentanyl citrate. (2.4, 2.5)
- Limit consumption to four or fewer units per day once successful dose is found. (2.5)
- When opioid therapy is no longer required, consider discontinuing oral transmucosal fentanyl citrate along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.7)

DOSAGE FORMS AND STRENGTHS

- Solid oral transmucosal lozenge: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Significant respiratory depression. (4)
- Management of acute or postoperative pain including headache/migraines and dental pain. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of oral transmucosal fentanyl citrate. (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue oral transmucosal fentanyl citrate if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of oral transmucosal fentanyl citrate in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of oral transmucosal fentanyl citrate in patients with impaired consciousness or coma. (5.13)

ADVERSE REACTIONS

Most common (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache,

dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact SpecGx LLC, at 1-800-778-7898 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid the use of mixed agonist/antagonist or partial agonist analgesics in patients who are already receiving a full opioid agonist analgesic (including oral transmucosal fentanyl citrate) because they may reduce analgesic effect of oral transmucosal fentanyl citrate or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended.
- Renal and Hepatic Impairment: Administer oral transmucosal fentanyl citrate with caution. (8.6)

See 17 for Medication Guide.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious, life-threatening and/or fatal respiratory depression has occurred in patients treated with oral transmucosal fentanyl citrate, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of oral transmucosal fentanyl citrate or following a dose increase *[see Warnings and Precautions (5.1)]*. The substitution of oral transmucosal fentanyl citrate for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.1)]*.

Due to the risk of respiratory depression, oral transmucosal fentanyl citrate is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients *[see Contraindications (4)]*.

Accidental Ingestion

Accidental ingestion of even one dose of oral transmucosal fentanyl citrate, especially by children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.2)]*.

Death has been reported in children who have accidentally ingested oral transmucosal fentanyl citrate. Oral transmucosal fentanyl citrate must be kept out of reach of children *[see Patient Counseling Information and How Supplied/Storage and Handling (16)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of oral transmucosal fentanyl citrate with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving oral transmucosal fentanyl citrate and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.3), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of oral transmucosal fentanyl citrate and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**

- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of oral transmucosal fentanyl citrate compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to oral transmucosal fentanyl citrate *[see Dosage and Administration (2.1)]*.**
- **When dispensing, do not substitute an oral transmucosal fentanyl citrate prescription for other fentanyl products.**

Addiction, Abuse, and Misuse

Oral transmucosal fentanyl citrate exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing oral transmucosal fentanyl citrate, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.6)]*.

Risk Evaluation and Mitigation Strategy (REMS)

Because of the risk for accidental exposure, misuse, abuse, addiction, and overdose, oral transmucosal fentanyl citrate is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS, pharmacies, outpatients, and healthcare professionals who prescribe to outpatients must enroll in the program. Inpatient pharmacies must develop policies and procedures to verify opioid tolerance in inpatients who require oral transmucosal fentanyl citrate while hospitalized *[see Warnings and Precautions (5.7)]*. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of oral transmucosal fentanyl citrate during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.8)]*.

1 INDICATIONS AND USAGE

Oral transmucosal fentanyl citrate is indicated for the management of breakthrough pain in cancer patients 16 years of age and older 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, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid. Patients must remain on around-the-clock opioids when taking oral transmucosal fentanyl citrate.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine and dental pain *[see Contraindications (4)]*.
- As a part of the TIRF REMS, oral transmucosal fentanyl citrate may be dispensed by outpatient pharmacies only to outpatients enrolled in the program *[see Warnings and Precautions (5.7)]*. For inpatient administration of oral transmucosal fentanyl citrate, patient and prescriber enrollment are not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe oral transmucosal fentanyl citrate for outpatients must enroll in the TIRF REMS and comply with the requirements of the REMS to ensure safe use of oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.7)]*.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with oral transmucosal fentanyl citrate and adjust the dosage accordingly *[see Warnings and Precautions (5.1)]*.
- Instruct patients and caregivers to take steps to store oral transmucosal fentanyl citrate securely and to properly dispose of unused oral transmucosal fentanyl citrate as soon as no longer needed *[see Warnings and Precautions (5.1, 5.2), Patient Counseling Information (17)].*
- Other TIRF formulations and oral transmucosal fentanyl citrate are not equivalent. DO NOT substitute an oral transmucosal fentanyl citrate prescription for any other TIRF formulation under any circumstances. Do not convert patients on a mcg per mcg basis from any other fentanyl product to oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.5)]*.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.1), Patient Counseling Information (17)]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose.

The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.4, 5.6)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosage

Individually titrate oral transmucosal fentanyl citrate to a dose that provides adequate analgesia and minimizes side effects. The initial dose of oral transmucosal fentanyl citrate to treat episodes of breakthrough cancer pain is always 200 mcg. The oral transmucosal fentanyl citrate unit should be consumed over 15 minutes. Patients should be prescribed an initial titration supply of six 200 mcg oral transmucosal fentanyl citrate units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose to prevent confusion and possible overdose.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 15 minutes after completion of the oral transmucosal fentanyl citrate unit (30 minutes after the start of the unit), patients may take ONLY ONE additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of oral transmucosal fentanyl citrate for any episode of breakthrough pain.

b. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with oral transmucosal fentanyl citrate.

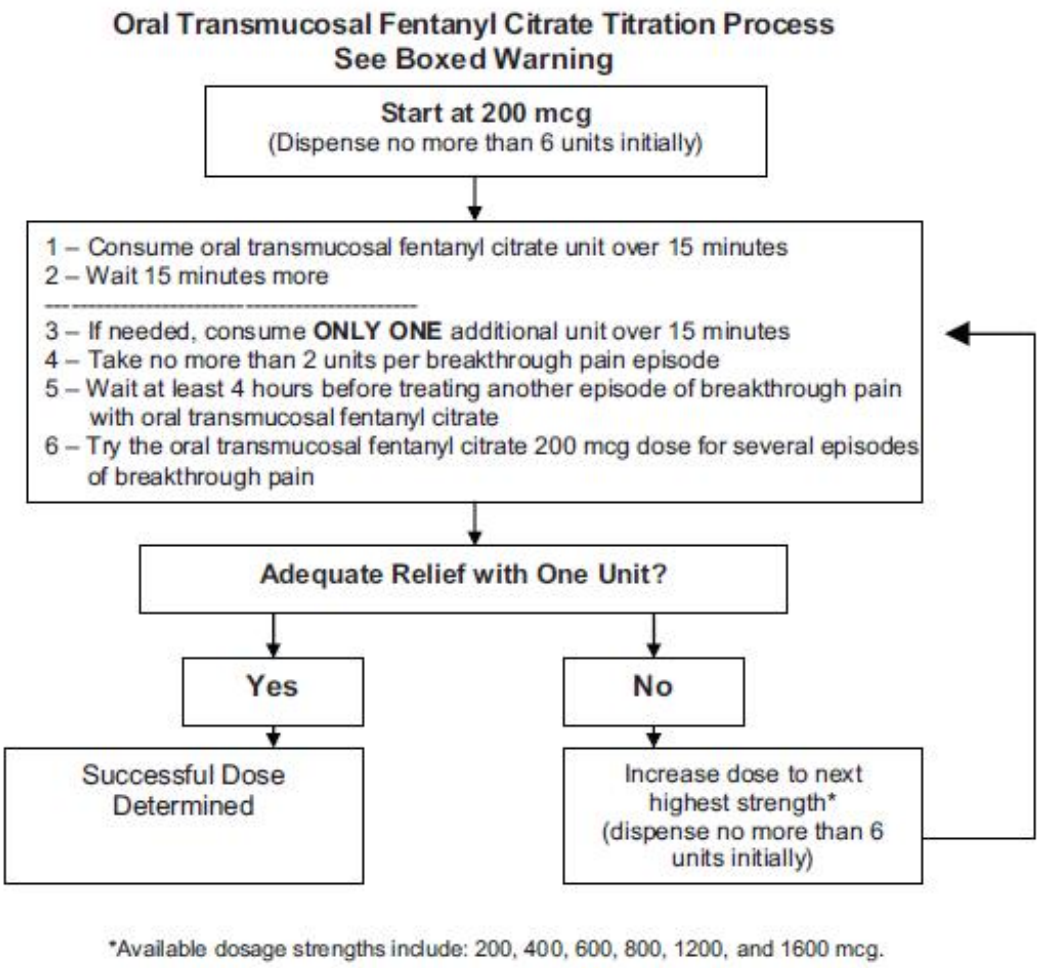
2.4 Dose Titration

From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia using a single oral transmucosal fentanyl citrate dosage unit per breakthrough cancer pain episode. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased. Patients should record their use of oral transmucosal fentanyl citrate over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

In cases where the breakthrough pain episode is not relieved 15 minutes after completion of the oral transmucosal fentanyl citrate unit (30 minutes after the start of the unit), patients may take ONLY ONE additional dose of the same strength for that

episode. Thus, patients should take a maximum of two doses of oral transmucosal fentanyl citrate for any breakthrough pain episode.

Patients must wait at least 4 hours before treating another episode of breakthrough pain with oral transmucosal fentanyl citrate. To reduce the risk of overdosing during titration, patients should have only one strength of oral transmucosal fentanyl citrate available at any one time.



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

2.5 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use ONLY ONE oral transmucosal fentanyl citrate unit of the appropriate strength per breakthrough pain episode.

b. On those occasions when the breakthrough pain episode is not relieved 15 minutes after completion of the oral transmucosal fentanyl citrate unit, patient may take ONLY ONE additional dose using the same strength for that episode.

c. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with oral transmucosal fentanyl citrate. Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day.

d. Dosage adjustment of oral transmucosal fentanyl citrate may be required in some

patients in order to continue to provide adequate relief of breakthrough pain.

e. Generally, the oral transmucosal fentanyl citrate dose should be increased only when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

f. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated.

2.6 Administration of Oral Transmucosal Fentanyl Citrate

Open the blister package with scissors immediately prior to product use. The patient should place the oral transmucosal fentanyl citrate unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The oral transmucosal fentanyl citrate unit should be sucked, not chewed. A unit dose of oral transmucosal fentanyl citrate, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed *[see Clinical Pharmacology (12.3)]*.

The oral transmucosal fentanyl citrate unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in oral transmucosal fentanyl citrate clinical trials. If signs of excessive opioid effects appear before the unit is consumed, remove the drug matrix from the patient's mouth immediately and decrease future doses.

2.7 Discontinuation of Oral Transmucosal Fentanyl Citrate

When opioid therapy is no longer required, consider discontinuing oral transmucosal fentanyl citrate along with a gradual downward tapering (titration) of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, oral transmucosal fentanyl citrate therapy can usually be discontinued immediately *[see Drug Abuse and Dependence (9.3)]*.

2.8 Disposal of Oral Transmucosal Fentanyl Citrate

After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.

- If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
- Dispose of handles in the child-resistant container (as described in steps 1 and 2) at least once a day.

If the temporary storage bottle provided as part of the oral transmucosal fentanyl citrate Child Safety Kit is available, partially consumed units may be stored in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Unopened units remaining from a prescription must be properly disposed as soon as they are no longer needed.

To dispose of the unused oral transmucosal fentanyl citrate units:

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

Do not flush the entire oral transmucosal fentanyl citrate units, oral transmucosal fentanyl citrate handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for SpecGx LLC (1-800-778-7898) or seek assistance from their local DEA office.

3 DOSAGE FORMS AND STRENGTHS

Solid oral transmucosal lozenge: Each dosage unit has white to off-white color and is a solid drug matrix on a handle. Each strength is marked on the individual solid drug matrix and the handle tag. Oral transmucosal fentanyl citrate is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Oral transmucosal fentanyl citrate is contraindicated in:
- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients *[see Indications and Usage (1)]; Warnings and Precautions (5.1) [see Indications and Usage (1)]*.
- Significant respiratory depression *[see Warnings and Precautions (5.1)]*.
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*.
- Known hypersensitivity to fentanyl or components of oral transmucosal fentanyl citrate (e.g., anaphylaxis, hypersensitivity) *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of

opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of oral transmucosal fentanyl citrate, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of oral transmucosal fentanyl citrate.

To reduce the risk of respiratory depression, proper dosing and titration of oral transmucosal fentanyl citrate are essential *[see Dosage and Administration (2)]*. Overestimating the oral transmucosal fentanyl citrate dosage can result in a fatal overdose with the first dose. The substitution of oral transmucosal fentanyl citrate for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.5)]*.

Oral transmucosal fentanyl citrate could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of even one dose of oral transmucosal fentanyl citrate, especially by children, can result in respiratory depression and death due to an overdose of fentanyl *[see Warnings and Precautions (5.1, 5.2)]*.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.7)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose
Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with oral transmucosal fentanyl citrate. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)].*

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone *[see Warnings and Precautions (5.4, 5.6), Patient Counseling Information (17)].*

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or

Exposure

Death has been reported in children who have accidentally ingested oral transmucosal fentanyl citrate.

Patients and their caregivers must be informed that oral transmucosal fentanyl citrate contains a medicine in an amount which can be fatal to a child. Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible *[see Patient Counseling Information (17)]*.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of oral transmucosal fentanyl citrate are provided in the oral transmucosal fentanyl citrate *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of oral transmucosal fentanyl citrate with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.1)]*, particularly when an inhibitor is added after a stable dose of oral transmucosal fentanyl citrate is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in oral transmucosal fentanyl citrate-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using oral transmucosal fentanyl citrate with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in oral transmucosal fentanyl citrate-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of oral transmucosal fentanyl citrate until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of oral transmucosal fentanyl citrate with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using oral transmucosal fentanyl citrate with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (including Alcohol)

Profound sedation, respiratory depression, coma, and death may result from the

concomitant use of oral transmucosal fentanyl citrate with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when oral transmucosal fentanyl citrate is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.5 Risk of Medication Errors

When prescribing, do not convert a patient to oral transmucosal fentanyl citrate from any other fentanyl product on a mcg per mcg basis as oral transmucosal fentanyl citrate and other fentanyl products are not equivalent on a microgram per microgram basis.

Oral transmucosal fentanyl citrate is not a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, do not substitute an oral transmucosal fentanyl citrate prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and oral transmucosal fentanyl citrate are not equivalent. Substantial differences exist in the pharmacokinetic profile of oral transmucosal fentanyl citrate compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of oral transmucosal fentanyl citrate for any other fentanyl product may result in a fatal overdose.

There are no safe conversion directions available for patients on any other fentanyl

products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of oral transmucosal fentanyl citrate should always be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.4)]*.

5.6 Addiction, Abuse, and Misuse

Oral transmucosal fentanyl citrate contains fentanyl, a Schedule II controlled substance. As an opioid, oral transmucosal fentanyl citrate exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed oral transmucosal fentanyl citrate. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing oral transmucosal fentanyl citrate, and monitor all patients receiving oral transmucosal fentanyl citrate for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as oral transmucosal fentanyl citrate, but use in such patients necessitates intensive counseling about the risks and proper use of oral transmucosal fentanyl citrate along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing oral transmucosal fentanyl citrate. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.7 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)

Because of the risk for accidental exposure, misuse, abuse, addiction, and overdose *[see Warnings and Precautions (5.6)],* oral transmucosal fentanyl citrate is available only through a restricted program called the TIRF REMS. Under the TIRF REMS, healthcare professionals who prescribe to outpatients, the outpatients themselves, and pharmacies are required to enroll in the program.

Notable requirements of the TIRF REMS are:

- Prescribers for outpatient use must be certified with the REMS program by enrolling and completing training. Prescribers must document opioid tolerance with every oral transmucosal fentanyl citrate prescription.
- Outpatients must be enrolled in the REMS program and must be opioid tolerant to receive oral transmucosal fentanyl citrate *[see Dosage and Administration (2.1)]*.
- Outpatient pharmacies must be certified with the REMS program and verify documentation of opioid tolerance with every oral transmucosal fentanyl citrate

prescription.
- Inpatient pharmacies must be certified with the REMS program and develop policies and procedures to verify opioid tolerance in inpatients who require oral transmucosal fentanyl citrate while hospitalized.
- Wholesalers and distributors must enroll in the REMS program and distribute only to certified pharmacies.

Further information, including a list of certified pharmacies and enrolled distributors, is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of oral transmucosal fentanyl citrate during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of oral transmucosal fentanyl citrate in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: Oral transmucosal fentanyl citrate-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.1)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.1)]*.

Monitor such patients closely, particularly when initiating and titrating oral transmucosal fentanyl citrate and when oral transmucosal fentanyl citrate is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.1)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of oral transmucosal fentanyl citrate with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle

relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue oral transmucosal fentanyl citrate if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

Oral transmucosal fentanyl citrate may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of oral transmucosal fentanyl citrate. In patients with circulatory shock, oral transmucosal fentanyl citrate may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of oral transmucosal fentanyl citrate in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), oral transmucosal fentanyl citrate may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with oral transmucosal fentanyl citrate.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of oral transmucosal fentanyl citrate in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions

Oral transmucosal fentanyl citrate is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in oral transmucosal fentanyl citrate may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The fentanyl in oral transmucosal fentanyl citrate may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during oral transmucosal fentanyl citrate therapy.

5.16 Risks of Driving and Operating Machinery

Oral transmucosal fentanyl citrate may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of oral transmucosal fentanyl citrate and know how they will react to the medication.

5.17 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use oral transmucosal fentanyl citrate with caution in patients with bradyarrhythmias.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.1)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.8)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of oral transmucosal fentanyl citrate has been evaluated in 257 opioid-

tolerant chronic cancer pain patients. The duration of oral transmucosal fentanyl citrate use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

The most serious adverse reactions associated with oral transmucosal fentanyl citrate are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock.

Because the clinical trials of oral transmucosal fentanyl citrate were designed to evaluate safety and efficacy in treating breakthrough cancer pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received oral transmucosal fentanyl citrate for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of oral transmucosal fentanyl citrate therapy, or cancer-related symptoms.

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. Table 1 lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schemes used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1. 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)

Percentage of Patients Reporting Event					
Dose Group	**200-600 mcg (n=230)**	**800-1400 mcg (n=138)**	**1600 mcg (n=54)**	**>1600 mcg (n=41)**	**Any Dose* (n=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

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

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

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

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia, migraine

Respiratory: Pharyngitis, cough increased

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

Body as a Whole: bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

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

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. Table 2 lists by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during the long-term extension study. Adverse reactions are listed in descending order of frequency within each body system.

Table 2. Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment (Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=98)	800-1400 mcg (n=83)	1600 mcg (n=53)	>1600 mcg (n=27)	Any Dose* (n=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

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following reactions not reflected in Table 2 occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

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

Cardiovascular: Deep thrombophlebitis, palpitation, vascular disorder

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

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

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

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

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

Skin and Appendages: Skin ulcer, alopecia

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

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

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

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

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

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

Hemic and Lymphatic: Bleeding time increased

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

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

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

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

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

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

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of oral transmucosal fentanyl citrate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Digestive:

- Dental decay: Dental decay, including dental caries, tooth loss, and gum line erosion.

Nervous System Disorders:

- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Endocrine Disorders:

- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.

Immune System Disorders:

- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in oral transmucosal fentanyl citrate.

General Disorders and Administration Site Conditions: Application site reactions including irritation, pain, and ulcer, and drug withdrawal syndrome.

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with oral transmucosal fentanyl citrate.

Table 3: Clinically Significant Drug Interactions with Oral Transmucosal Fentanyl Citrate

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of oral transmucosal fentanyl citrate and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of oral transmucosal fentanyl citrate is achieved *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention:	If concomitant use is necessary, consider dosage reduction of oral transmucosal fentanyl citrate until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the oral transmucosal fentanyl citrate dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of oral transmucosal fentanyl citrate and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inducer, as the effects of

	the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the oral transmucosal fentanyl citrate dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider oral transmucosal fentanyl citrate dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.4, 5.6)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.10)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue oral transmucosal fentanyl citrate if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone),

	monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.10)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.1)]*.
Intervention:	The use of oral transmucosal fentanyl citrate is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of oral transmucosal fentanyl citrate and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphrine
Muscle Relaxants	
Clinical Impact:	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of oral transmucosal fentanyl citrate and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.4)].*
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when oral transmucosal

intervention.	fentanyl citrate is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.8)]*. Available data with oral transmucosal fentanyl citrate in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.8)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Oral transmucosal fentanyl citrate is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including oral transmucosal fentanyl citrate, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor.

Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data
In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Animal Data
Fentanyl (25, 50, or 100 mcg/kg) citrate was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6 to 17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (the no observed effect level of 50 mcg/kg is equivalent to 0.7 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6 to 18). Maternal toxicity was noted at doses >100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 3.5 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison).

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.2 times the 1600 mcg dose of oral transmucosal fentanyl citrate on a mg/m^2 basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (1 times the 1600 mcg dose of oral transmucosal fentanyl citrate based on a mg/m^2 basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 3 times the human dose of 1600 mcg oral transmucosal fentanyl citrate per pain episode on a mg/m^2 basis and produced mean steady-state plasma levels that are 3.4 times higher than the mean C_{max} observed following administration of 1600 mcg dose of oral transmucosal fentanyl citrate in humans.

In a postnatal development study, pregnant rats were treated from GD 6 through Lactation Day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100, and 400 mcg/kg). Maternal toxicity was noted at doses >100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at >100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is 0.6 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison.

8.2 Lactation

Risk Summary
Fentanyl is present in breast milk. One published lactation study reports a relative infant

dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with oral transmucosal fentanyl citrate.

Clinical Considerations
Monitor infants exposed to oral transmucosal fentanyl citrate through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below 16 years of age have not been established.

In a clinical study, 15 opioid-tolerant pediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with oral transmucosal fentanyl citrate. The study was too small to allow conclusions on safety and efficacy in this patient population. Twelve of the fifteen opioid-tolerant children and adolescents aged 5 to 15 years in this study received oral transmucosal fentanyl citrate at doses ranging from 200 mcg to 600 mcg. The mean (CV%; range) dose-normalized (to 200 mcg) C_{max} and AUC_{0-8} values were 0.87 ng/mL (51%; 0.42-1.30) and 4.54 ng•h/mL (42%; 2.37-6.0), respectively, for children ages 5 to <11 years old (N = 3) and 0.68 ng/mL (72%; 0.15-1.44) and 8.38 (192%; 0.84-50.78), respectively, for children ages ≥11 to <16 y (N = 9).

8.5 Geriatric Use

Of the 257 patients in clinical studies of oral transmucosal fentanyl citrate in breakthrough cancer pain, 61 (24%) were 65 years of age and older, while 15 (6%) were 75 years of age and older. Those patients over the age of 65 years were titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in oral transmucosal fentanyl citrate clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, exercise caution when individually titrating oral transmucosal fentanyl citrate in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of oral transmucosal fentanyl citrate slowly in geriatric

patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of oral transmucosal fentanyl citrate in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

8.7 Sex

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Oral transmucosal fentanyl citrate contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

Oral transmucosal fentanyl citrate contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine oxycodone, oxymorphone, and tapentadol. Oral transmucosal fentanyl citrate can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.6)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical

records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Oral transmucosal fentanyl citrate, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of Oral Transmucosal Fentanyl Citrate
Oral transmucosal fentanyl citrate is for oral transmucosal use only. Abuse of oral transmucosal fentanyl citrate poses a risk of overdose and death. The risk is increased with concurrent abuse of oral transmucosal fentanyl citrate with alcohol and other central nervous system depressants.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation
Acute overdose with oral transmucosal fentanyl citrate can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose

situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose
In case of overdose, priorities are: removal of the oral transmucosal fentanyl citrate unit, if still in the mouth, the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in oral transmucosal fentanyl citrate, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

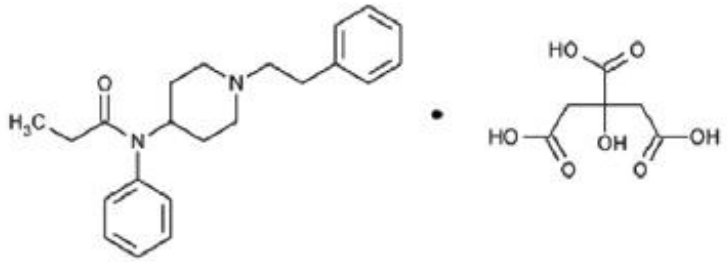
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Oral transmucosal fentanyl citrate lozenge is a solid formulation of fentanyl, an opioid agonist, intended for oral transmucosal administration. Oral transmucosal fentanyl citrate is formulated as a white to off-white solid drug matrix on a handle that is fracture resistant (ABS plastic) under normal conditions when used as directed.

Oral transmucosal fentanyl citrate is designed to be dissolved slowly in the mouth to facilitate transmucosal absorption. The handle allows the oral transmucosal fentanyl citrate unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

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



Inactive Ingredients: Raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the Central Nervous System
The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and electrical stimulation.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle
Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating, and/or orthostatic

hypotension.

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals.

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.3, 2.4, 2.5)]*.

Respiratory System
All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of oral transmucosal fentanyl citrate. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by

causing rigidity in the muscles of respiration *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4), Adverse Reactions (6), and Overdosage (10)]*.

12.3 Pharmacokinetics

Absorption

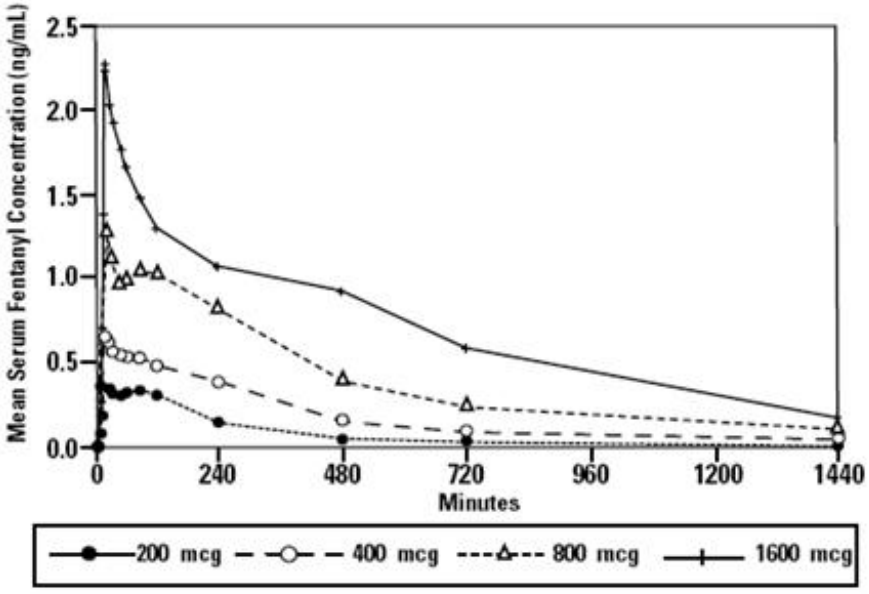
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary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

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

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

Dose proportionality among four of the available strengths of oral transmucosal fentanyl citrate (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects (n=11). Mean serum fentanyl levels following these four doses of oral transmucosal fentanyl citrate are shown in Figure 1. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0\rightarrow\infty}$ increased in a dose-dependent manner that is approximately proportional to the oral transmucosal fentanyl citrate administered.

Figure 1.
Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of Oral Transmucosal Fentanyl Citrate



The pharmacokinetic parameters of the four strengths of oral transmucosal fentanyl citrate tested in the dose-proportionality study are shown in Table 4. The mean C_{max} ranged from 0.39 to 2.51 ng/mL. The median time of maximum plasma concentration (T_{max}) across these four doses of oral transmucosal fentanyl citrate varied from 20 to 40 minutes (range of 20 to 480 minutes) as measured after the start of administration.

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving 200, 400, 800, and 1600 mcg Units of Oral Transmucosal Fentanyl Citrate

Pharmacokinetic Parameter	**200 mcg**	**400 mcg**	**800 mcg**	**1600 mcg**
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)

* **Based on arterial blood samples.**

Distribution

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

Elimination

The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after oral transmucosal fentanyl citrate administration is about 7 hours.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies *[see Drug Interactions (7)]*.

Excretion

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 1.13 and 2.7 times the exposure of a single human dose of 1600 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis
Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility
In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 4.0 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 2.7 times the exposure of a single human dose of 1600 mcg per pain episode, based on an AUC comparison.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for oral transmucosal fentanyl citrate.

14 CLINICAL STUDIES

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

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of oral transmucosal fentanyl citrate to treat their

breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200, and 1600 mcg). A “successful” dose was defined as a dose where one unit of oral transmucosal fentanyl citrate could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects. In these studies 11% of patients withdrew due to adverse reactions and 14% withdrew due to other reasons.

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

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 5.

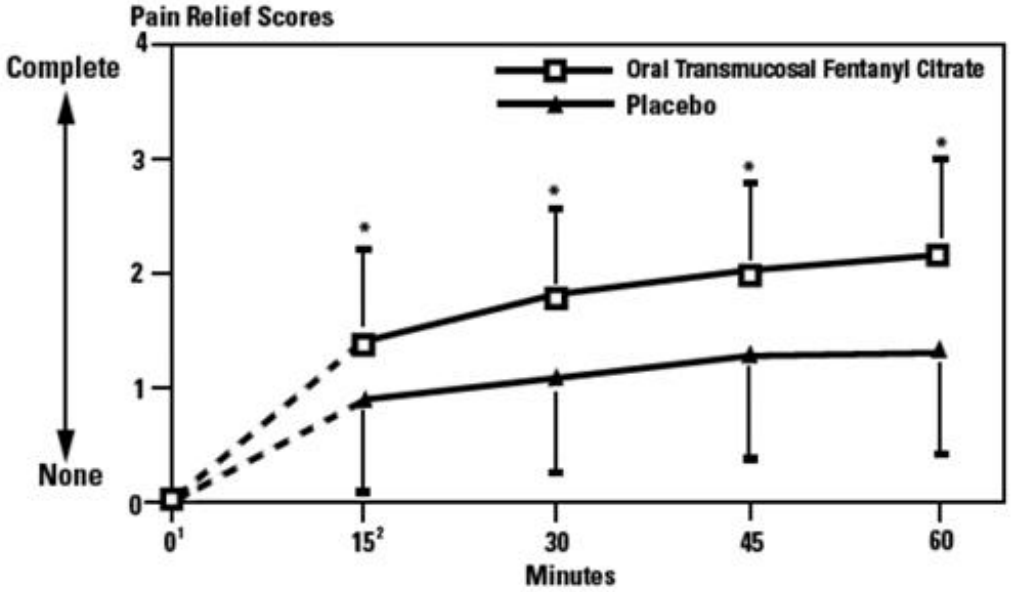
Table 5. Successful Dose of Oral Transmucosal Fentanyl Citrate Following Initial Titration

Oral Transmucosal Fentanyl Citrate Dose	**Total No. (%) (N=92)**
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean +/- SD	789 +/- 468 mcg

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

Oral transmucosal fentanyl citrate was administered beginning at Time 0 minutes and produced more pain relief compared with placebo at 15, 30, 45, and 60 minutes as measured after the start of administration (See Figure 2). The differences were statistically significant.

Figure 2.
Pain Relief (PR) Scores (Mean±SD) During the Double-Blind Phase − All Patients with Evaluable Episodes on Both Oral Transmucosal Fentanyl Citrate and Placebo (N=86)



16 HOW SUPPLIED/STORAGE AND HANDLING

Oral transmucosal fentanyl citrate is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

Each dosage unit has a white to off-white color. Each individual solid drug matrix is marked with “FENTANYL” and the strength of the unit (“200 MCG”, “400 MCG”, “600 MCG”, “800 MCG”, “1200 MCG”, or “1600 MCG”). The dosage strength is also marked on the handle tag, the blister package and the carton. See blister package and carton for product information.

Dosage Strength (fentanyl base)	**Carton/Blister Package Color**	**NDC Number**	**Imprint**
200 mcg	Gray	NDC 0406-9202-30	FENTANYL, 200 MCG
400 mcg	Blue	NDC 0406-9204-30	FENTANYL, 400 MCG
600 mcg	Orange	NDC 0406-9206-30	FENTANYL, 600 MCG
800 mcg	Purple	NDC 0406-9208-30	FENTANYL, 800 MCG
1200 mcg	Green	NDC 0406-9212-30	FENTANYL, 1200 MCG
1600 mcg	Burgundy	NDC 0406-9216-30	FENTANYL, 1600 MCG

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

Store at 20° to 25°C (68° to 77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use [see USP Controlled Room Temperature]. Protect oral transmucosal fentanyl citrate from freezing and moisture. Do not use if the blister package has been opened.

Store oral transmucosal fentanyl citrate securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide)*.

Storage and Disposal of Unused and Used Oral Transmucosal Fentanyl Citrate *[see Medication Guide / Instructions for Use]*.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store oral transmucosal fentanyl citrate securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.6), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving oral transmucosal fentanyl citrate unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Disposal of Used Oral Transmucosal Fentanyl Citrate Units:
Instruct patients on proper disposal of completely used and partially used oral transmucosal fentanyl citrate units as follows:

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

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

Disposal of Unopened Oral Transmucosal Fentanyl Citrate Units When No Longer Needed:
Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused oral transmucosal fentanyl citrate units:

- Remove the oral transmucosal fentanyl citrate unit from its blister package using

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

Do not flush the entire oral transmucosal fentanyl citrate units, oral transmucosal fentanyl citrate handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of oral transmucosal fentanyl citrate are provided in the oral transmucosal fentanyl citrate *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for SpecGx LLC (1-800-778-7898) or seek assistance from their local DEA office.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting oral transmucosal fentanyl citrate or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Warnings and Precautions (5.1)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with oral transmucosal fentanyl citrate. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone’s effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:
- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Accidental Ingestion

- Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure *[see Warnings and Precautions (5.2)]*.
- Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)].*
- Instruct patients to take steps to store oral transmucosal fentanyl citrate securely and to dispose of unused oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.2, 5.7), Patient Counseling Information, Disposal of Used Oral Transmucosal Fentanyl Citrate Units]*.
- Instruct patients and caregivers to keep both used and unused oral transmucosal fentanyl citrate out of the reach of children *[see Warnings and Precautions (5.2)].*
- Inform patients and their caregivers that, in the event that a unit is not completely consumed, it must be properly disposed as soon as possible *[see Warnings and Precautions (5.2), Patient Counseling Information, Disposal of Used Oral Transmucosal Fentanyl Citrate Units].*

Oral Transmucosal Fentanyl Citrate Child Safety Kit
Provide patients and their caregivers who have children in the home or visiting with an oral transmucosal fentanyl citrate Child Safety Kit, which contains educational materials and safe interim storage containers to help patients store oral transmucosal fentanyl citrate and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, healthcare professionals can call 1-800-223-1499.

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)
Inform patients and caregivers that potentially fatal additive effects may occur if oral transmucosal fentanyl citrate is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Addiction, Abuse, and Misuse
Inform patients that the use of oral transmucosal fentanyl citrate, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.6)]*. Instruct patients not to share oral transmucosal fentanyl citrate with others and to take steps to protect oral transmucosal fentanyl citrate from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS
Oral transmucosal fentanyl citrate is available only through a restricted program called the Transmucosal Immediate Release Fentanyl (TIRF) REMS *[see Warnings and Precautions (5.7)]*. Inform the patient of the following notable requirements:

- Outpatients must be enrolled in the REMS program
- Patients must be opioid-tolerant to receive ACTIQ

Oral transmucosal fentanyl citrate is available only from certified pharmacies participating in this program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients are required to enroll in the program. Inpatient pharmacies must develop policies and

procedures to verify opioid tolerance in inpatients who require oral transmucosal fentanyl citrate while hospitalized *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.10), Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking oral transmucosal fentanyl citrate while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking oral transmucosal fentanyl citrate *[see Warnings and Precautions (5.10); Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Important Administration Instructions *[see Dosage and Administration (2)]*

- Instruct patients not to take oral transmucosal fentanyl citrate for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and that oral transmucosal fentanyl citrate is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.
- Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take oral transmucosal fentanyl citrate.
- Instruct patients that, if the breakthrough pain episode is not relieved 15 minutes after finishing the oral transmucosal fentanyl citrate unit, they may take only one additional unit of oral transmucosal fentanyl citrate using the same strength for that episode. Thus, patients should take no more than two units of oral transmucosal fentanyl citrate for any breakthrough pain episode.
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with oral transmucosal fentanyl citrate.
- Instruct patients NOT to share oral transmucosal fentanyl citrate and that sharing oral transmucosal fentanyl citrate with anyone else could result in the other individual’s death due to overdose.
- Make patients aware that oral transmucosal fentanyl citrate contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking oral transmucosal fentanyl citrate.
- Instruct patients to use oral transmucosal fentanyl citrate exactly as prescribed by their doctor and not to take oral transmucosal fentanyl citrate more often than prescribed.

Hypotension
Inform patients that oral transmucosal fentanyl citrate may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)].*

Anaphylaxis
Inform patients that anaphylaxis have been reported with ingredients contained in oral transmucosal fentanyl citrate. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of oral transmucosal fentanyl citrate during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that oral transmucosal fentanyl citrate can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery
Inform patients that oral transmucosal fentanyl citrate may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Dental Decay
Because each oral transmucosal fentanyl citrate unit contains approximately 2 grams of sugar (hydrated dextrates), frequent consumption may increase the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Post-marketing reports of dental decay have been received in patients taking oral transmucosal fentanyl citrate *[see Adverse Reactions (6.2)]*. In some of these patients, dental decay occurred despite reported routine oral hygiene. As dental decay in cancer patients may be multi-factorial, patients using oral transmucosal fentanyl citrate should

consult their dentist to ensure appropriate oral hygiene.

Diabetic Patients
Advise diabetic patients that oral transmucosal fentanyl citrate contains approximately 2 grams of sugar per unit.

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Mallinckrodt™
Pharmaceuticals

Medication Guide

Oral Transmucosal Fentanyl Citrate (orˊ əl ● tranz mu-kōˊ s'l ● fĕnˊ tə-nĭl ● sĭtˊ rāt)
oral transmucosal lozenge, CII

IMPORTANT:
Do not use oral transmucosal fentanyl citrate unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.
Keep oral transmucosal fentanyl citrate in a safe place away from children.
Get emergency medical help right away if:

- **a child takes oral transmucosal fentanyl citrate. Oral transmucosal fentanyl citrate can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed oral transmucosal fentanyl citrate uses it.**
- **an adult who is not already taking opioids around-the-clock, uses oral transmucosal fentanyl citrate.**

These are medical emergencies that can cause death. If possible, remove oral transmucosal fentanyl citrate from the mouth.

Oral transmucosal fentanyl citrate is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. Oral transmucosal fentanyl citrate is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use oral transmucosal fentanyl citrate if you are not opioid tolerant.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse,

and misuse that can lead to death.

Important information about oral transmucosal fentanyl citrate:

- **Get emergency help or call 911 right away if you take too much oral transmucosal fentanyl citrate (overdose).** When you first start taking oral transmucosal fentanyl citrate, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking oral transmucosal fentanyl citrate with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your oral transmucosal fentanyl citrate. They could die from taking it. Selling or giving away oral transmucosal fentanyl citrate is against the law.
- Store oral transmucosal fentanyl citrate securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.
- If you stop taking your around-the-clock opioid pain medicine for your cancer pain, you must stop using oral transmucosal fentanyl citrate. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
- Oral transmucosal fentanyl citrate is available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS). To receive oral transmucosal fentanyl citrate, you must:
  - talk to your healthcare provider
  - understand the benefits and risks of oral transmucosal fentanyl citrate
  - agree to all of the instructions
  - sign the Patient Enrollment Form
- Oral transmucosal fentanyl citrate is only available at pharmacies that are part of the TIRF REMS. Your healthcare provider can help you locate a pharmacy closest to your home where you can have your oral transmucosal fentanyl citrate prescription filled.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take oral transmucosal fentanyl citrate if:

- You are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- You are allergic to any of the ingredients in oral transmucosal fentanyl citrate. See the end of this Medication Guide for a complete list of ingredients in oral transmucosal fentanyl citrate.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking oral transmucosal fentanyl citrate, tell your healthcare provider if you have a history of:

- troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- head injury, seizures
- problems urinating
- slow heart rate or other heart problems
- liver, kidney, thyroid problems
- low blood pressure
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems
- diabetes. Each oral transmucosal fentanyl citrate unit contains about ½ teaspoon (2 grams) of sugar.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of oral transmucosal fentanyl citrate during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Oral transmucosal fentanyl citrate passes into breast milk and may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking oral transmucosal fentanyl citrate with certain other medicines can cause serious side effects that could lead to death.

When taking oral transmucosal fentanyl citrate:

- Do not change your dose. Take oral transmucosal fentanyl citrate exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use oral transmucosal fentanyl citrate.**
- Finish the unit completely in 15 minutes to get the most relief. If you finish oral transmucosal fentanyl citrate too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using oral transmucosal fentanyl citrate but you should not drink or eat anything while using oral transmucosal fentanyl citrate.
- You must not use more than 2 units of oral transmucosal fentanyl citrate during each episode of breakthrough cancer pain:
  - Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
  - If your breakthrough cancer pain is not relieved 15 minutes after you finished the oral transmucosal fentanyl citrate unit, use **only 1** more unit of oral transmucosal fentanyl citrate at this time.
  - If your breakthrough pain does not get better after the second unit of oral

transmucosal fentanyl citrate, call your healthcare provider for instructions. **Do not use another unit of oral transmucosal fentanyl citrate at this time.**

- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with oral transmucosal fentanyl citrate.
- It is important for you to keep taking your around-the-clock opioid pain medicine.
- Talk to your healthcare provider if your dose of oral transmucosal fentanyl citrate does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of oral transmucosal fentanyl citrate needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before oral transmucosal fentanyl citrate is completely dissolved, remove oral transmucosal fentanyl citrate from your mouth.
- Do not stop taking oral transmucosal fentanyl citrate without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- After you stop taking, or when oral transmucosal fentanyl citrate is no longer needed, see "**How should I dispose of oral transmucosal fentanyl citrate units when they are no longer needed?**" for proper disposal of oral transmucosal fentanyl citrate.
- Dispose of expired, unwanted, or unused oral transmucosal fentanyl citrate by following the "**How should I dispose of oral transmucosal fentanyl citrate units when they are no longer needed?**" sections of this Medication Guide below. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.
- **DO NOT** Drive or operate heavy machinery, until you know how oral transmucosal fentanyl citrate affects you. Oral transmucosal fentanyl citrate can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with oral transmucosal fentanyl citrate may cause you to overdose and die.
- **DO NOT Switch from oral transmucosal fentanyl citrate to other medicines that contain fentanyl without talking to your healthcare provider.** The amount of fentanyl in a dose of oral transmucosal fentanyl citrate is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of oral transmucosal fentanyl citrate that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of oral transmucosal fentanyl citrate:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, weakness, anxiety, depression, rash, trouble sleeping. Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- Oral transmucosal fentanyl citrate contains sugar. Cavities and tooth decay can happen in people taking oral transmucosal fentanyl citrate. When taking oral transmucosal fentanyl citrate, you should talk to your dentist about proper care of

your teeth.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have used too much oral transmucosal fentanyl citrate or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more oral transmucosal fentanyl citrate until you have talked to your healthcare provider.**

These are not all the possible side effects of oral transmucosal fentanyl citrate. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

How should I store oral transmucosal fentanyl citrate?

- **Always keep oral transmucosal fentanyl citrate in a safe place away from children and from anyone for whom it has not been prescribed.** Protect oral transmucosal fentanyl citrate from theft.
  - You can use the oral transmucosal fentanyl citrate Child Safety Kit to help you store oral transmucosal fentanyl citrate and your other medicines out of the reach of children. It is very important that you use the items in the oral transmucosal fentanyl citrate Child Safety Kit to help protect the children in your home or visiting your home.
  - If you were not offered a Child Safety Kit when you received your medicine, call Mallinckrodt Pharmaceutical Child Safety Kit Request Line at 1-800-223-1499 to request one.

  The oral transmucosal fentanyl citrate Child Safety Kit contains important information on the safe storage and handling of oral transmucosal fentanyl citrate.

  The Child Safety Kit includes:

  - **A child-resistant lock that** you use to secure the storage space where you keep oral transmucosal fentanyl citrate (See Figure 1).

Figure 1

  - **A portable locking pouch** for you to keep a small supply of oral transmucosal fentanyl citrate nearby. The rest of your oral transmucosal fentanyl citrate must be kept in a locked storage space.
    - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See Figure 2).

Figure 2

- **A child-resistant temporary storage bottle** (See Figure 3)**.**

Figure 3

- Store oral transmucosal fentanyl citrate at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze oral transmucosal fentanyl citrate.
- **Keep oral transmucosal fentanyl citrate in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use oral transmucosal fentanyl citrate.**
- Keep oral transmucosal fentanyl citrate dry.

  How should I dispose of oral transmucosal fentanyl citrate units when they are no longer needed?

  Disposing of oral transmucosal fentanyl citrate units after use:

  Partially used oral transmucosal fentanyl citrate units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed oral transmucosal fentanyl citrate. **You must properly dispose of the oral transmucosal fentanyl citrate handle right away after use even if there is little or no medicine left on it.**

  After you have finished the oral transmucosal fentanyl citrate unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

  If **any** medicine remains on the used oral transmucosal fentanyl citrate unit after you have finished:
- Place the used oral transmucosal fentanyl citrate unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See Figure 4).

Figure 4

<u>Temporary Storage of Used Oral Transmucosal Fentanyl Citrate Units:</u>

- If you did not finish the entire oral transmucosal fentanyl citrate unit and you cannot dissolve the medicine under hot running water right away, put the used

oral transmucosal fentanyl citrate unit in the temporary storage bottle that you received in the oral transmucosal fentanyl citrate Child Safety Kit. Place the oral transmucosal fentanyl citrate unit into the bottle and secure the cap. **Never leave unused or partially used oral transmucosal fentanyl citrate units where children or pets can get to them** (See Figure 5)**.**

Figure 5

Disposing of Used Oral Transmucosal Fentanyl Citrate Units from the Temporary Storage Bottle:

You must dispose of all used oral transmucosal fentanyl citrate units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See Figure 6).

Figure 6

2. Remove one oral transmucosal fentanyl citrate unit from the temporary storage bottle. Hold the oral transmucosal fentanyl citrate by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each oral transmucosal fentanyl citrate handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused oral transmucosal fentanyl citrate units, oral transmucosal fentanyl citrate handles, or blister packages down the toilet.

Disposing of unopened oral transmucosal fentanyl citrate units: Dispose of any unopened oral transmucosal fentanyl citrate units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all oral transmucosal fentanyl citrate from the locked storage space (See Figure 7).

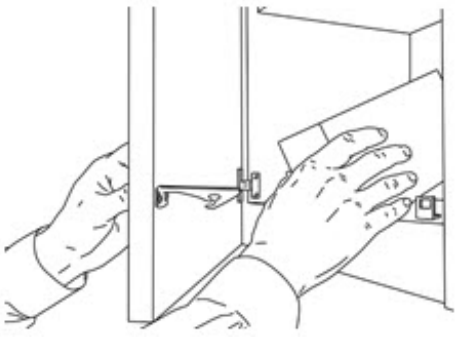


Figure 7

2. Remove one oral transmucosal fentanyl citrate unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See Figures 8A and 8B).

Figure 8A

Figure 8B

3. Hold oral transmucosal fentanyl citrate by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See Figures 9A and 9B).

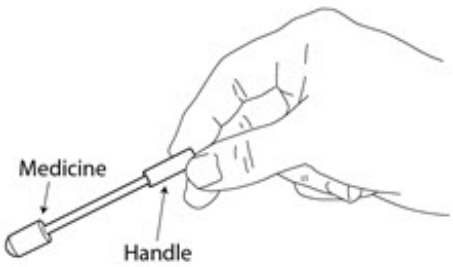


Figure 9A

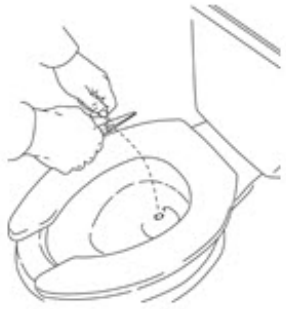


Figure 9B

4. Throw the handle away in a place that is out of the reach of children (See Figure 10).

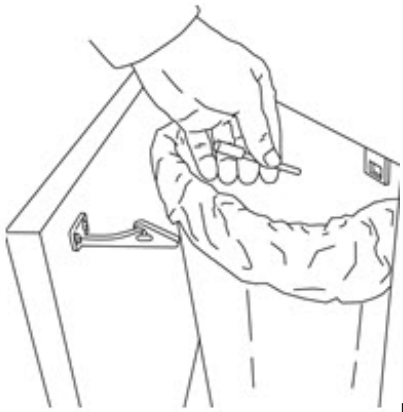


Figure 10

5. Repeat steps 1 through 4 for each oral transmucosal fentanyl citrate unit.
6. Flush the toilet twice after the medicine ends from 5 oral transmucosal fentanyl citrate units have been cut off (See Figure 11). Do not flush more than 5 oral transmucosal fentanyl citrate units at a time.

Figure 11

- Do not flush entire unused oral transmucosal fentanyl citrate units, oral transmucosal fentanyl citrate handles, or blister packages down the toilet.

If you need help with the disposal of oral transmucosal fentanyl citrate, call SpecGx LLC, Product Monitoring at
1-800-778-7898, or call your local Drug Enforcement Agency (DEA) office.

General information about oral transmucosal fentanyl citrate

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use oral transmucosal fentanyl citrate only for the**

purpose for which it was prescribed. Do not give oral transmucosal fentanyl citrate to other people, even if they have the same symptoms you have. Oral transmucosal fentanyl citrate can harm other people and even cause death. Sharing oral transmucosal fentanyl citrate is against the law.
This Medication Guide summarizes the most important information about oral transmucosal fentanyl citrate. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about oral transmucosal fentanyl citrate that is written for healthcare professionals. For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients of oral transmucosal fentanyl citrate?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

Patient Instructions for Use

Before you use oral transmucosal fentanyl citrate, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use oral transmucosal fentanyl citrate the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use oral transmucosal fentanyl citrate.

When you get an episode of breakthrough cancer pain, use the dose of oral transmucosal fentanyl citrate prescribed by your healthcare provider as follows:

- You may drink some water before using oral transmucosal fentanyl citrate but you should not drink or eat anything while using oral transmucosal fentanyl citrate.
- Each unit of oral transmucosal fentanyl citrate is sealed in its own blister package (See Figure 12). **Do not open the blister package until you are ready to use oral transmucosal fentanyl citrate.**

Figure 12

- When you are ready to use oral transmucosal fentanyl citrate, cut open the package using scissors. Peel back the blister backing, and remove the oral transmucosal fentanyl citrate unit (See Figures 13A and 13B). The end of the unit printed with “FENTANYL” and the strength number of the unit (“200MCG”, “400MCG”, “600MCG”, “800MCG”, “1200MCG”, or “1600MCG”) is the medicine end that is to be placed in your mouth. Hold the oral transmucosal fentanyl citrate unit by the handle (See Figure 14).

Figure 13A

Figure 13B

Figure 14

1. Place the medicine end of the oral transmucosal fentanyl citrate unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the oral transmucosal fentanyl citrate unit around in your mouth, especially along the inside of your cheeks (See Figure 15).

Figure 15

3. Twirl the handle often.
4. Finish the oral transmucosal fentanyl citrate unit completely over 15 minutes to get the most relief. If you finish oral transmucosal fentanyl citrate too quickly, you will swallow more of the medicine and get less relief.

5. Do not bite or chew oral transmucosal fentanyl citrate. You will get less relief for your breakthrough cancer pain.

- If you cannot finish all of the medicine on the oral transmucosal fentanyl citrate unit and cannot dissolve the medicine under hot tap water right away, immediately put the oral transmucosal fentanyl citrate unit in the temporary storage bottle for safe keeping (See Figure 16).
  - Place the oral transmucosal fentanyl citrate unit into the bottle and secure the cap. You must properly dispose of the oral transmucosal fentanyl citrate unit as soon as you can.

Figure 16

See "**How should I dispose of oral transmucosal fentanyl citrate units when they are no longer needed?**" for proper disposal of oral transmucosal

fentanyl citrate.
Manufactured by:
SpecGx LLC
Webster Groves, MO 63119 USA
Revised 03/2021
1110000
Mallinckrodt™
This Medication Guide has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 200 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9202-30

30 Units

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

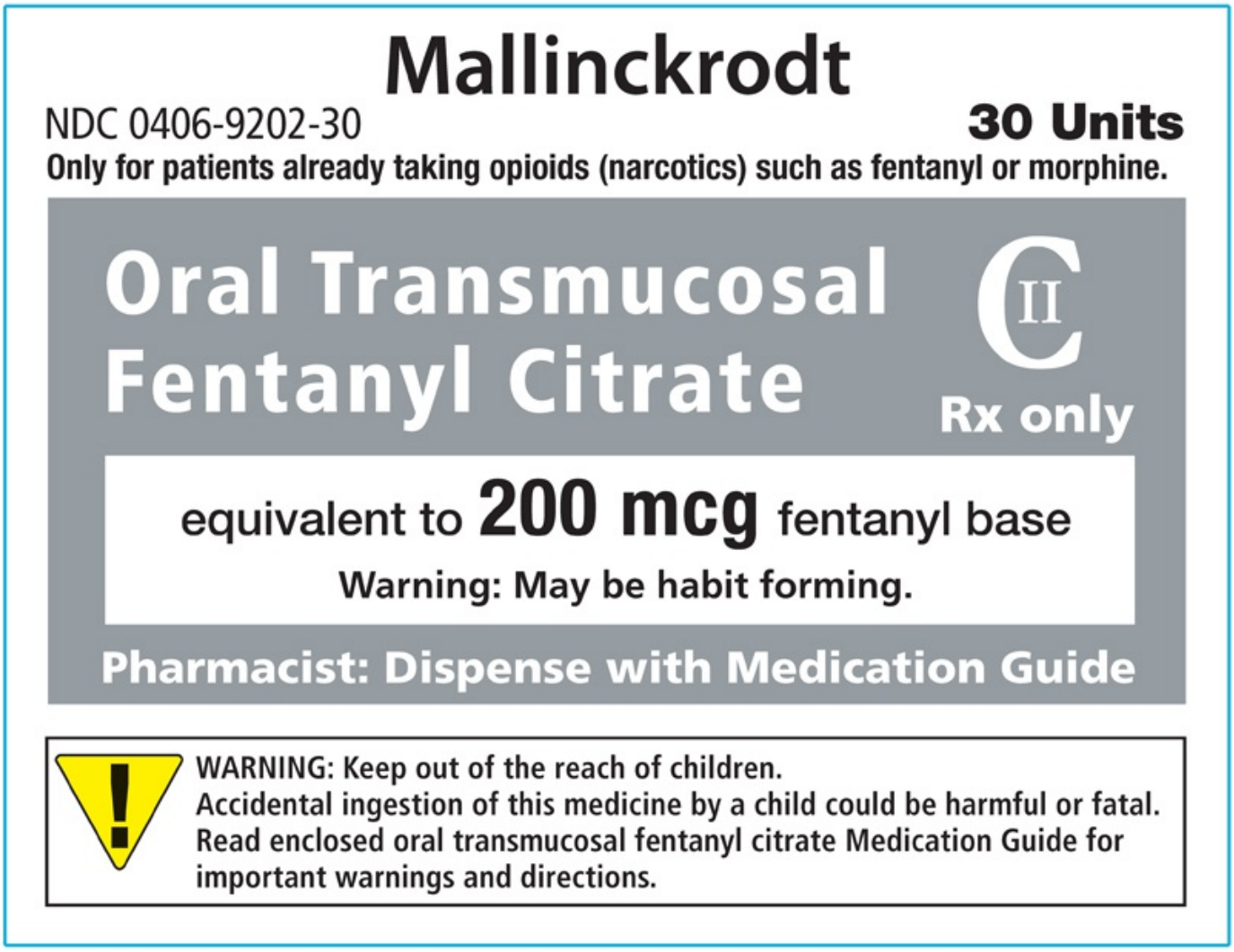
Oral Transmucosal Fentanyl Citrate

CII
Rx only

equivalent to **200 mcg** fentanyl base
Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed oral transmucosal fentanyl citrate Medication Guide for important warnings and directions.



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 400 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9204-30

30 Units

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

Oral Transmucosal Fentanyl Citrate

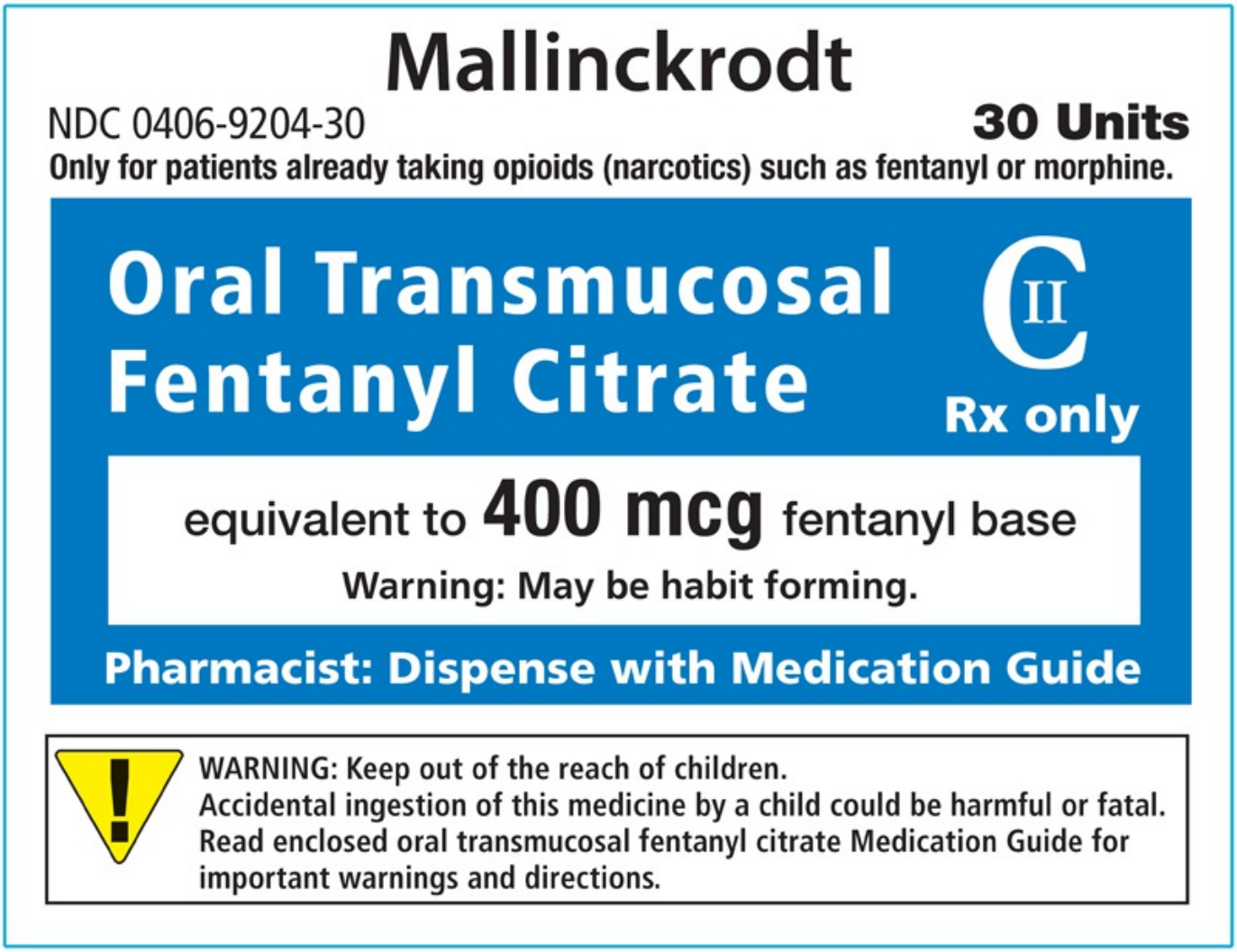
CII
Rx only

equivalent to **400 mcg** fentanyl base
Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed oral transmucosal fentanyl citrate Medication Guide for

important warnings and directions.



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 600 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9206-30

30 Units

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

Oral Transmucosal Fentanyl Citrate

CII
Rx only

equivalent to **600 mcg** fentanyl base
Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

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

Read enclosed oral transmucosal fentanyl citrate Medication Guide for important warnings and directions.

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 800 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9208-30

30 Units

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

Oral Transmucosal Fentanyl Citrate

CII
Rx only

equivalent to **800 mcg** fentanyl base
Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed oral transmucosal fentanyl citrate Medication Guide for important warnings and directions.

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 1200 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9212-30

30 Units

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

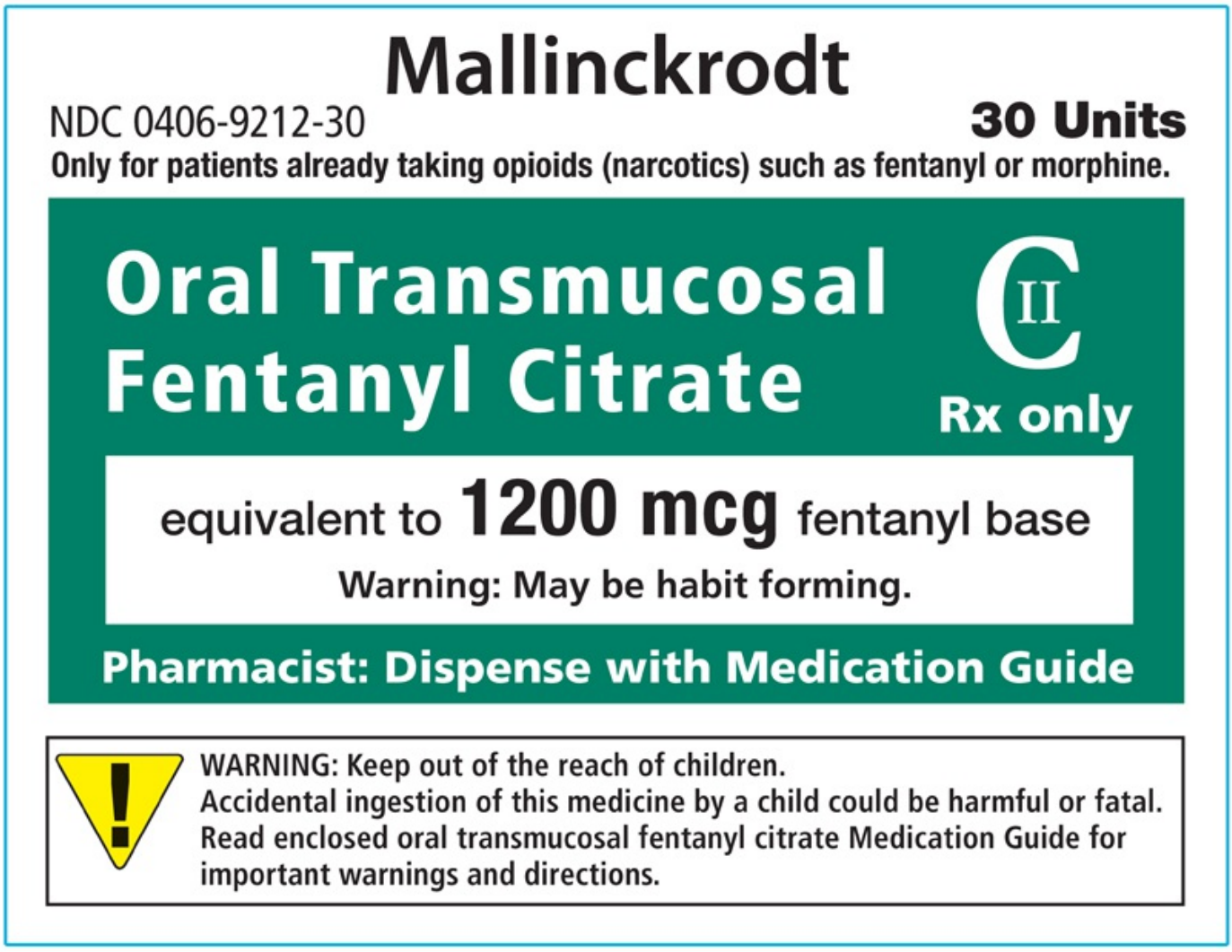
Oral Transmucosal Fentanyl Citrate

CII
Rx only

equivalent to **1200 mcg** fentanyl base
Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed oral transmucosal fentanyl citrate Medication Guide for important warnings and directions.



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 1600 mcg, 30 Unit Carton

Mallinckrodt

NDC 0406-9216-30

30 Units

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

Oral Transmucosal Fentanyl Citrate

CII
Rx only

equivalent to **1600 mcg** fentanyl base

Warning: May be habit forming.

Pharmacist: Dispense with Medication Guide

WARNING: Keep out of the reach of children.
Accidental ingestion of this medicine by a child could be harmful or fatal.
Read enclosed oral transmucosal fentanyl citrate Medication Guide for important warnings and directions.

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9202
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	200 ug

Inactive Ingredients	
Ingredient Name	**Strength**
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;200;MCG
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9202-30	30 in 1 CARTON	10/30/2009	01/31/2025
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078907	10/30/2009	01/31/2025

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9204
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	400 ug

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;400;MCG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9204-30	30 in 1 CARTON	10/30/2009	12/31/2024
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078907	10/30/2009	12/31/2024

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9206
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	600 ug

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;600;MCG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9206-30	30 in 1 CARTON	10/30/2009	12/31/2024
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078907	10/30/2009	12/31/2024

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9208
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	800 ug

Inactive Ingredients	
Ingredient Name	**Strength**
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics			
Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;800;MCG
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0406-9208-30	30 in 1 CARTON	10/30/2009	02/28/2025
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing	Application Number or Monograph	Marketing Start	Marketing End

Category	Citation	Date	Date
ANDA	ANDA078907	10/30/2009	02/28/2025

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9212
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	1200 ug

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;1200;MCG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9212-30	30 in 1 CARTON	10/30/2009	10/31/2024
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078907	10/30/2009	10/31/2024

FENTANYL CITRATE

fentanyl citrate lozenge

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0406-9216
Route of Administration	TRANSMUCOSAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL CITRATE (UNII: MUN5LYG46H) (FENTANYL - UNII:UF599785JZ)	FENTANYL	1600 ug

Inactive Ingredients

Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
SUCROSE (UNII: C151H8M554)	
STARCH, CORN (UNII: O8232NY3SJ)	
DEXTRATES (UNII: G263MI44RU)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM PHOSPHATE, DIBASIC, UNSPECIFIED FORM (UNII: GR686LBA74)	
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)	
ALCOHOL (UNII: 3K9958V90M)	
WATER (UNII: 059QF0KO0R)	
SHELLAC (UNII: 46N107B71O)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
AMMONIA (UNII: 5138Q19F1X)	

Product Characteristics

Color	white (to off-white)	**Score**	no score
Shape	BULLET	**Size**	19mm
Flavor	RASPBERRY	**Imprint Code**	FENTANYL;1600;MCG
Contains			

Packaging

			Marketing Start	Marketing End

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0406-9216-30	30 in 1 CARTON	10/30/2009	02/28/2025
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078907	10/30/2009	02/28/2025

Labeler - SpecGx LLC (080679498)

Establishment

Name	Address	ID/FEI	Business Operations
SpecGx LLC		163205300	analysis(0406-9216, 0406-9212, 0406-9202, 0406-9204, 0406-9206, 0406-9208) , manufacture(0406-9216, 0406-9212, 0406-9202, 0406-9204, 0406-9206, 0406-9208)

Revised: 10/2023 SpecGx LLC