HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Oral Transmucosal Fentanyl Citrate (OTFC) safely and effectively. See full prescribing information for OTFC.

Oral Transmucosal Fentanyl Citrate (OTFC) Lozenge, CII

Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, OTFC is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)**
- **Keep out of reach of children. (5.3)**
- **Use with CYP 3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to OTFC. (2.1, 5.1)**
- **When dispensing, do not substitute with any other fentanyl products. (5.1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Oral Transmucosal Fentanyl Citrate (OTFC) is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies and distributors are required to enroll in the program. (5.10)**

---------------- RECENT MAJOR CHANGES ----------------

Indications and Usage (1)	12/2011
Warnings and Precautions – TIRF REMS Access Program (5.10)	12/2011

---------------- INDICATIONS AND USAGE ----------------

Oral Transmucosal Fentanyl Citrate (OTFC) 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. (1)

Limitations of Use:

OTFC may be dispensed only to patients enrolled in the TIRF REMS Access program. (1)

------------ DOSAGE AND ADMINISTRATION ------------

- Patients must require and use around-the-clock opioids when taking OTFC. (1)
- Initial dose of Oral Transmucosal Fentanyl Citrate (OTFC): 200 mcg. Prescribe an initial supply of six 200 mcg OTFC units. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single OTFC dosage unit per breakthrough cancer pain episode. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with OTFC. (2.3)
- Limit consumption to four or fewer units per day once successful dose is found. (2.3)

------------ DOSAGE FORMS AND STRENGTHS ------------

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

---------------- CONTRAINDICATIONS ----------------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraines and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl, or components of OTFC. (4)

--------------- WARNINGS AND PRECAUTIONS ---------------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Full and partially consumed Oral Transmucosal Fentanyl Citrate (OTFC) units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("OTFC Child Safety Kit"). (5.3)
- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate OTFC cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO_2 retention. (5.6, 5.7)

---------------- 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 Par Pharmaceutical at 1-800-828-9393 option 2 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------------- DRUG INTERACTIONS ----------------

- See Boxed Warning and Warnings and Precautions. (5.4, 7)

------------ USE IN SPECIFIC POPULATIONS ------------

- Administer Oral Transmucosal Fentanyl Citrate (OTFC) with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2013

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Initial Dose
2.2 Dose Titration
2.3 Maintenance Dosing
2.4 Administration of OTFC
2.5 Discontinuation of OTFC
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Respiratory Depression
5.2 Important Information Regarding Prescribing and Dispensing
5.3 Patient/Caregiver Instructions
5.4 Additive CNS Depressant Effects
5.5 Effects on Ability to Drive and Use Machines
5.6 Chronic Pulmonary Disease
5.7 Head Injuries and Increased Intracranial Pressure
5.8 Cardiac Disease
5.9 MAO Inhibitors
5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Renal or Hepatic Impairment
8.7 Gender
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse and Addiction
9.3 Dependence
10 OVERDOSAGE
10.1 Clinical Presentation
10.2 Immediate Management
10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person
10.4 Treatment of Overdose in Opioid-Tolerant Patients
10.5 General Considerations for Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Storage and Handling
16.2 Disposal of OTFC
16.3 How Supplied
17 PATIENT COUNSELING INFORMATION
17.1 Patient/Caregiver Instructions
17.2 Dental Care
17.3 Diabetic Patients
17.4 OTFC Child Safety Kit
17.5 Disposal of Used OTFC Units
17.6 Disposal of Unopened OTFC Units When No Longer Needed
MEDICATION GUIDE

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with Oral Transmucosal Fentanyl Citrate (OTFC), including following use in opioid non-tolerant patients and improper dosing. The substitution of OTFC for any other fentanyl product may result in fatal overdose.

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

Death has been reported in children who have accidentally ingested Oral Transmucosal Fentanyl Citrate (OTFC). OTFC must be kept out of reach of children. *[see Patient Counseling Information (17.3) and How Supplied/Storage and Handling(16.1)]*

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

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

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

ABUSE POTENTIAL

Oral Transmucosal Fentanyl Citrate (OTFC) contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. OTFC can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OTFC in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, OTFC is available only through a restricted program required by the Food and Drug Administration, called the Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies and distributors must enroll in the program. [*See Warnings and Precautions (5.10)*] Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Oral Transmucosal Fentanyl Citrate (OTFC) 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 around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking OTFC.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, OTFC is contraindicated in the management of acute or postoperative pain.

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

Limitations of Use:

As a part of the TIRF REMS Access Program, OTFC may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.10)]*. For inpatient administration of OTFC (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe OTFC on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of OTFC *[see Warnings and Precautions (5.10)]*.

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

2.1 Initial Dose

Individually titrate Oral Transmucosal Fentanyl Citrate (OTFC) to a dose that provides adequate analgesia and minimizes side effects. The initial dose of OTFC to treat episodes of breakthrough cancer pain is **always** 200 mcg. The OTFC unit should be consumed over 15 minutes. Patients should be prescribed an initial titration supply of six 200 mcg OTFC 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.

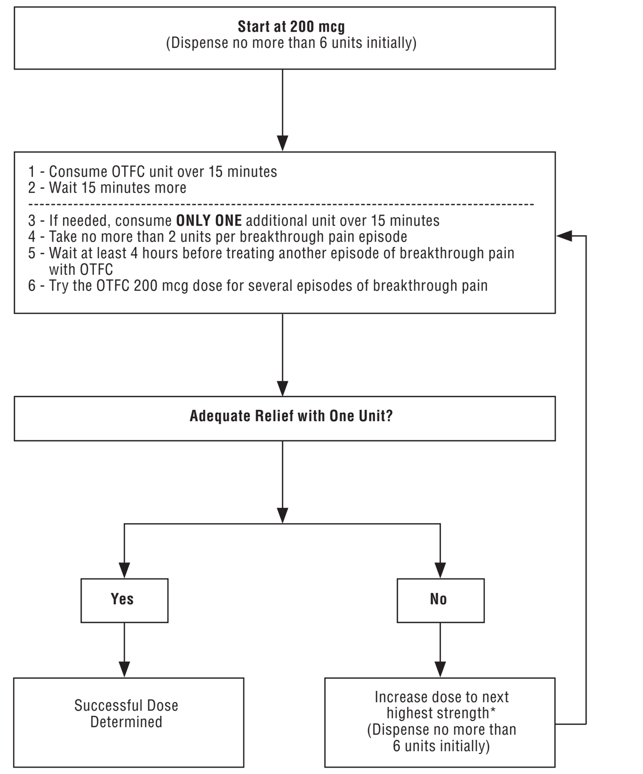
2.2 Dose Titration

From this initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single OTFC 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 OTFC 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 OTFC 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 OTFC for any breakthrough pain episode.

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

OTFC Titration Process
See Boxed Warning



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

2.3 Maintenance Dosing

Once titrated to an effective dose, patients should generally use **ONLY ONE** Oral Transmucosal Fentanyl Citrate (OTFC) unit of the appropriate strength per breakthrough pain episode.

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

Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with OTFC. 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.

Dosage adjustment of OTFC may be required in some patients in order to continue to provide adequate relief of breakthrough pain.

Generally, the OTFC 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.

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.

2.4 Administration of OTFC

Open the blister package with scissors immediately prior to product use. The patient should place the Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC unit should be sucked, not chewed. A unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed [*see Clinical Pharmacology (12.3)*].

The OTFC unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in OTFC 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.

2.5 Discontinuation of OTFC

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

3 DOSAGE FORMS AND STRENGTHS

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 (OTFC) is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths [*see How Supplied/Storage and Handling (16.3)*].

4 CONTRAINDICATIONS

OTFC is contraindicated in opioid non-tolerant patients. OTFC is contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

OTFC is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of OTFC.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning - WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in OTFC. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 Important Information Regarding Prescribing and Dispensing

When prescribing, DO NOT convert a patient to OTFC from any other fentanyl product on a mcg per mcg basis as OTFC and other fentanyl products are not equivalent on a microgram per microgram basis.

OTFC is NOT a generic version of fentanyl buccal tablets (Fentora®). **When dispensing, DO NOT substitute an OTFC prescription for fentanyl buccal tablets (Fentora®) prescription under any circumstances. Fentanyl buccal tablets (Fentora®) and OTFC are not equivalent.** Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products including fentanyl buccal tablets (Fentora®) that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of OTFC 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 OTFC should **always** be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [*see Dosage and Administration (2.2)*].

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that Oral Transmucosal Fentanyl Citrate (OTFC) contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested OTFC. 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 How Supplied/Storage and Handling, (16.1, 16.2), Patient Counseling Information (17.3), and Medication Guide*].

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.

OTFC could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

5.4 Additive CNS Depressant Effects

The concomitant use of OTFC with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., respiratory depression, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [*see Drug Interactions (7)*].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of OTFC if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate OTFC with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of OTFC may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer OTFC with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.8 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use OTFC with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors

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

5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose *[See Drug Abuse and Dependence (9)]*, OTFC is available only through a restricted program called the TIRF REMS Access program. Under the TIRF REMS Access program, outpatients, healthcare professionals who prescribe for outpatient use, pharmacies and distributors must enroll in the program. For inpatient administration, (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of OTFC, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access Program are:

- Healthcare professionals, who prescribe OTFC for outpatient use, must review the prescriber educational materials for the TIRF REMS Access Program, enroll in the program, and commit to comply with the REMS requirements.
- To receive OTFC, outpatients must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense OTFC must enroll in the program, and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute OTFC must enroll in the program, and distribute only to authorized pharmacies.

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety of Oral Transmucosal Fentanyl Citrate (OTFC) has been evaluated in 257 opioid-tolerant chronic cancer pain patients. The duration of OTFC use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

The adverse reactions seen with OTFC are typical opioid side effects. Frequently, these adverse reactions will cease or decrease in intensity with continued use of OTFC, as the patient is titrated to the proper dose. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including OTFC are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

Because the clinical trials of OTFC 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 OTFC 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 OTFC therapy, or cancer-related symptoms. Adverse reactions are included regardless of causality or severity.

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.

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of OTFC that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. **Table 1** lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse 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)

Dose Group	Percentage of Patients Reporting Event				
	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

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

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: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

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

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

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

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

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

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

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. **Table 2** lists by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse 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, migraine, palpitation, vascular disorder

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

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

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

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

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

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

Skin and Appendages: Skin ulcer, alopecia

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

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

The following 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, injection site pain, mucous membrane disorder, neck rigidity

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

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

Hemic and Lymphatic: Bleeding time increased

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

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

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

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

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

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

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

6.2 Postmarketing Experience

Adverse reactions are reported voluntarily from a population of uncertain size, and, therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to OTFC.

The following adverse reactions have been identified during post-approval use of OTFC (which contains approximately 2 grams of sugar per unit):

Digestive: Dental decay of varying severity including dental caries, tooth loss, and gum line erosion.

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

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when OTFC is given concurrently with agents that affect CYP3A4 activity. The concomitant use of OTFC with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving OTFC concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, thus should be avoided.

Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.

Concomitant use of OTFC with an MAO inhibitor, or within 14 days of discontinuation, is not recommended [*see Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Oral Transmucosal Fentanyl Citrate (OTFC) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

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.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for OTFC.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m^2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore do not use OTFC during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use OTFC in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using OTFC.

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 OTFC. 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 OTFC 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 to 1.30) and 4.54 ng·h/mL (42%; 2.37 to 6.0), respectively, for children ages 5 to <11 years old (N = 3) and 0.68 ng/mL (72%; 0.15 to 1.44) and 8.38 (192%; 0.84 to 50.78), respectively, for children ages ≥11 to <16 y (N = 9).

8.5 Geriatric Use

Of the 257 patients in clinical studies of OTFC 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 OTFC 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 OTFC in elderly patients to provide adequate efficacy while minimizing risk.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of OTFC 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 Gender

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. Oral Transmucosal Fentanyl Citrate (OTFC) may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of OTFC to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [*see How Supplied/Storage and Handling (16.1, 16.2)*].

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians 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 addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since OTFC may be diverted for nonmedical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

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

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

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

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of Oral Transmucosal Fentanyl Citrate (OTFC) overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being respiratory depression [*see Clinical Pharmacology (12.2)*].

10.2 Immediate Management

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

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

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

10.4 Treatment of Overdose in Opioid-Tolerant Patients

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

10.5 General Considerations for Overdose

Management of severe OTFC overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of respiratory depression or apnea, assist or control ventilation, and administer oxygen as indicated.

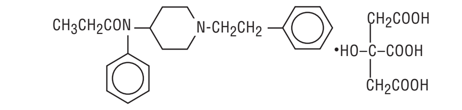
Although muscle rigidity interfering with respiration has not been seen following the use of OTFC, this is possible with fentanyl and other opioids. If it occurs, manage it by using assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

11 DESCRIPTION

Oral Transmucosal Fentanyl Citrate (OTFC) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. OTFC 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.

OTFC is designed to be dissolved slowly in the mouth to facilitate transmucosal absorption. The handle allows the OTFC 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: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol, and purified shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia

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

In 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. As a result, the dose of Oral Transmucosal Fentanyl Citrate (OTFC) should be individually titrated to achieve the desired effect [*see Dosage and Administration (2.2)*].

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 both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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).

Gastrointestinal System

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 is delayed in the small intestine 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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

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 OTFC. 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. Fentanyl depresses the cough reflex as a result of its CNS activity. 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. Therefore, physicians and other healthcare providers should be aware of this potential complication [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Contraindications (4), Warnings and Precautions (5.2), Adverse Reactions (6), and Overdosage (10)*].

12.3 Pharmacokinetics

Absorption

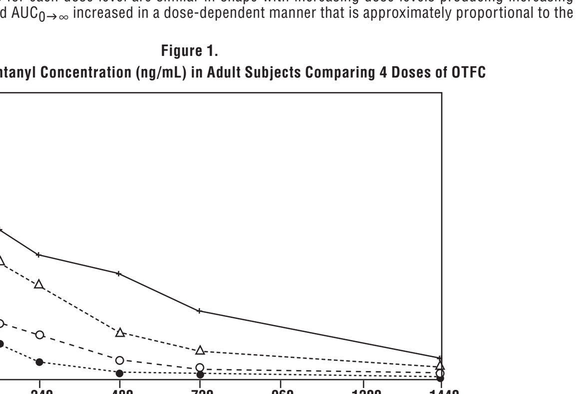
The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary 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 (OTFC) 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 OTFC is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of OTFC, 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 OTFC (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 OTFC 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 OTFC administered.

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



The pharmacokinetic parameters of the four strengths of OTFC tested in the dose-proportionality study are shown in **Table 3**. 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 OTFC varied from 20 to 40 minutes (range of 20 to 480 minutes) as measured after the start of administration.

Table 3.
Pharmacokinetic Parameters* in Adult Subjects
Receiving 200, 400, 800, and 1600 mcg Units of OTFC

Pharmacokinetic Parameter	200 mcg	400 mcg	800 mcg	1600 mcg
T_{max}, minute median (range)	40 (20 to 120)	25 (20 to 240)	25 (20 to 120)	20 (20 to 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.

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)*].

Elimination

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

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.

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 OTFC.

14 CLINICAL STUDIES

Oral Transmucosal Fentanyl Citrate (OTFC) 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 OTFC 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 OTFC 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 OTFC 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 OTFC 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 4**.

Table 4.
Successful Dose of OTFC Following Initial Titration

OTFC 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.

OTFC 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.

MEDICATION GUIDE
Oral Transmucosal Fentanyl Citrate (FEN ta nil SIT rayt) Lozenge CII (OTFC)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:
Do not use Oral Transmucosal Fentanyl Citrate (OTFC) 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 (OTFC) in a safe place away from children.

Get emergency medical help right away if:
- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC 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) Access program. To receive OTFC, you must:
- talk to your healthcare provider
- understand the benefits and risks of OTFC
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC 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.
- OTFC 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 OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:
- **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.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:
- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about 1/2 teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:
- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:
- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- 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 OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC 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 OTFC unit, use **only 1** more unit of OTFC at this time.
  - If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC 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 OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about OTFC?**"
   Call your healthcare provider or get emergency medical help right away if you:
   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC 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 OTFC until you have talked to your healthcare provider.**
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, 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.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:
- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without

treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC 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 PAR PHARMACEUTICAL at 1-800-828-9393 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

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

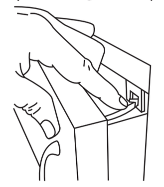


Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC 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**).

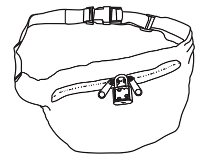


Figure 2

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

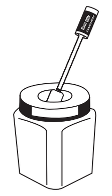


Figure 3

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

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

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

After you have finished the OTFC 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 OTFC unit after you have finished:

- Place the used OTFC 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**).

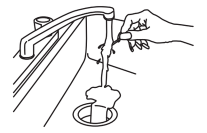


Figure 4

<u>Temporary Storage of Used OTFC Units</u>:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

<u>Disposing of Used OTFC Units from the Temporary Storage Bottle</u>:

You must dispose of all used OTFC 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**).

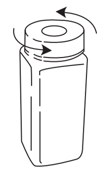


Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC 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 OTFC 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 OTFC units, OTFC handles, or blister packages down the toilet.

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

1. Remove all OTFC from the locked storage space (See **Figure 7**).

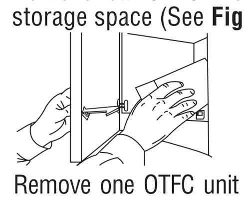


Figure 7

2. Remove one OTFC 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**).

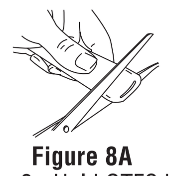


Figure 8A

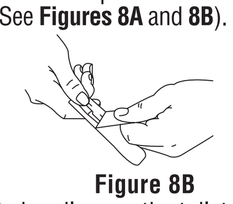


Figure 8B

3. Hold OTFC 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**).

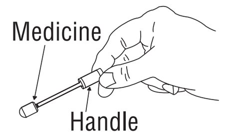


Figure 9A

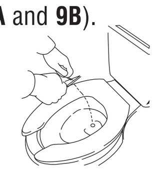


Figure 9B

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

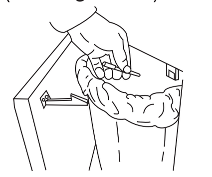


Figure 10

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

Figure 11

- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have**. OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC 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 (OTFC)?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, 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 OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

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

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See **Figure12**). **Do not open the blister package until you are ready to use OTFC.**

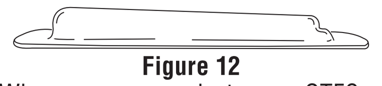


Figure 12

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

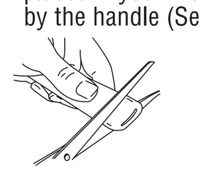


Figure 13A

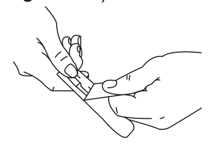


Figure 13B

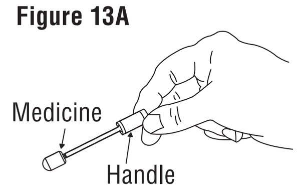


Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC 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 OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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PAR PHARMACEUTICAL COMPANIES, INC.
Chestnut Ridge, NY 10977

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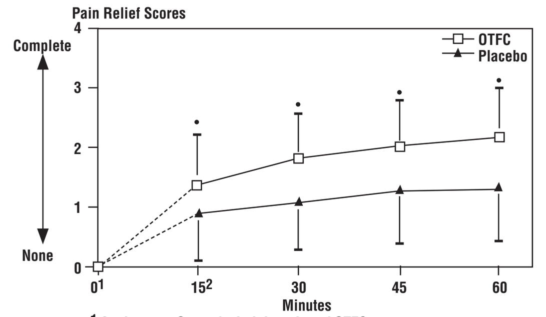
MG459-01-1/61-06

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



[1] 0 minutes = Start of administration of OTFC
[2] 15 minutes = First time to measure pain relief

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in OTFC can be fatal to a child. Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)*].

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature] until ready to use. Protect OTFC from freezing and moisture. Do not use if the blister package has been opened.

16.2 Disposal of OTFC

Patients must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child-resistant blister package, yet may contain enough medicine to be fatal to a child [*see Patient Counseling Information (17.5)*].

A temporary storage bottle is provided as part of the Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit [*see Patient Counseling Information (17.4)*]. This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the *Medication Guide.*

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in *Patient Counseling Information (17.6)* and in the *Medication Guide*. If additional assistance is required, call PAR PHARMACEUTICAL at 1-800-828-9393.

16.3 How Supplied

Oral Transmucosal Fentanyl Citrate (OTFC) 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.

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied as white to off-white, round cylindrical shaped lozenges attached to a fracture resistant plastic handle, as:

200 mcg: Imprinted Fentanyl over 200 mcg in blue ink, debossed with 1 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

400 mcg: Imprinted Fentanyl over 400 mcg in blue ink, debossed with 2 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

600 mcg: Imprinted Fentanyl over 600 mcg in blue ink, debossed with 3 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

800 mcg: Imprinted Fentanyl over 800 mcg in blue ink, debossed with 4 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

1200 mcg: Imprinted Fentanyl over 1200 mcg in blue ink, debossed with 5 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

1600 mcg: Imprinted Fentanyl over 1600 mcg in blue ink, debossed with 6 on the convex (top) side and flat on the other (bottom) side.
30 Units (10 x 3 Blisters)

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide*).

17.1 Patient/Caregiver Instructions

- Before initiating treatment with Oral Transmucosal Fentanyl Citrate (OTFC), explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time OTFC is dispensed because new information may be available.
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive OTFC.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding OTFC or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access Program, prescribers must review the contents of the OTFC Medication Guide with every patient before initiating treatment with OTFC.
  - Advise the patient that OTFC is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug
  - Advise the patient that only enrolled healthcare providers may prescribe OTFC.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of OTFC.
  - Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program.
- **Patients and their caregivers must be instructed that children exposed to OTFC are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*See How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.2 and 5.3) and Medication Guide for specific patient instructions.*]
- Provide patients and their caregivers with a *Medication Guide* and review it with them each time OTFC is dispensed because new information may be available.
- Instruct patients and their caregivers to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [*see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3), and Patient Counseling Information (17.5)*].
- Instruct patients not to take OTFC 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 OTFC 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 OTFC.
- Instruct patients that, if the breakthrough pain episode is not relieved 15 minutes after finishing the OTFC unit, they may take **ONLY ONE ADDITIONAL UNIT OF OTFC USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take no more than two units of OTFC for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with OTFC.
- Instruct patients NOT to share OTFC and that sharing OTFC with anyone else could result in the other individual's death due to overdose.
- Make patients aware that OTFC contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in OTFC, fentanyl, is a drug that some people abuse. OTFC should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking OTFC.
- Instruct patients to use OTFC exactly as prescribed by their doctor and not to take OTFC more often than prescribed.
- Caution patients that OTFC can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.
- Warn patients to not combine OTFC with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Inform female patients that if they become pregnant or plan to become pregnant during treatment with OTFC, they should ask their doctor about the effects that OTFC (or any medicine) may have on them and their unborn children.
- 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.

17.2 Dental Care

Because each OTFC unit contains approximately 2 grams of sugar, 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.

Postmarketing reports of dental decay have been received in patients taking OTFC [*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 OTFC should consult their dentist to ensure appropriate oral hygiene.

17.3 Diabetic Patients

Advise diabetic patients that OTFC contains approximately 2 grams of sugar per unit.

17.4 OTFC Child Safety Kit

Provide patients and their caregivers who have children in the home or visiting with an Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit, which contains educational materials and safe interim storage containers to help patients store OTFC and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, healthcare professionals can call PAR PHARMACEUTICAL at 1-800-828-9393.

17.5 Disposal of Used OTFC Units

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

1. After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2. If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3. 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 OTFC unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

17.6 Disposal of Unopened OTFC 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 OTFC units:

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

Do not flush the entire OTFC units, OTFC handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it [*see How Supplied/Storage and Handling (16.1)*].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of OTFC are provided in the OTFC *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 PAR PHARMACEUTICAL (1-800-828-9393) or seek assistance from their local DEA office.

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MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt) Lozenge CII
(OTFC)

200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:
Do not use Oral Transmucosal Fentanyl Citrate (OTFC) 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 (OTFC) in a safe place away from children.

Get emergency medical help right away if:
- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC 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) Access program. To receive OTFC, you must:

- talk to your healthcare provider
- understand the benefits and risks of OTFC
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC 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.
- OTFC 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 OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **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.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- 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 OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC 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 OTFC unit, use **only 1** more unit of OTFC at this time.
  - If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC 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 OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See **"What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:
   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC 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 OTFC until you have talked to your healthcare provider.**
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, 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.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC 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 PAR PHARMACEUTICAL at 1-800-828-9393 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

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

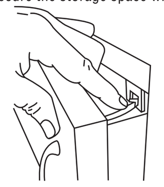

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC 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**).

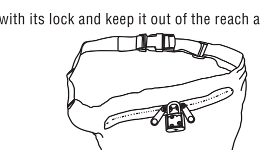

Figure 2

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

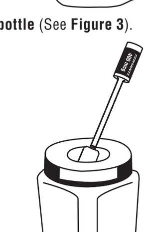

Figure 3

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

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

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

After you have finished the OTFC 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 OTFC unit after you have finished:

- Place the used OTFC 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**).

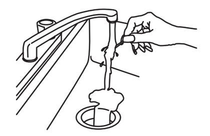

Figure 4

<u>Temporary Storage of Used OTFC Units</u>:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

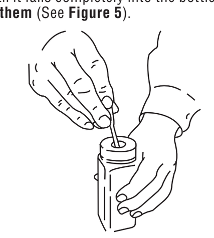

Figure 5

<u>Disposing of Used OTFC Units from the Temporary Storage Bottle</u>:

You must dispose of all used OTFC 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**).

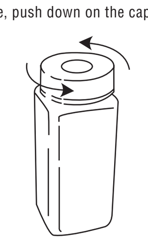

Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC 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 OTFC 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 OTFC units, OTFC handles, or blister packages down the toilet.

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

1. Remove all OTFC from the locked storage space (See **Figure 7**).

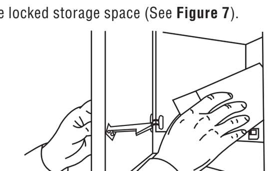

Figure 7

2. Remove one OTFC 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**).

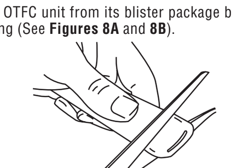

Figure 8A

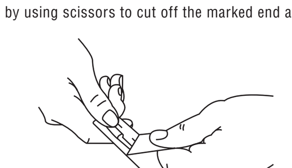

Figure 8B

3. Hold OTFC 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**).

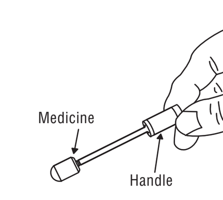

Figure 9A

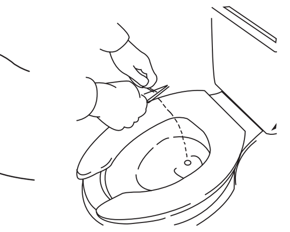

Figure 9B

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

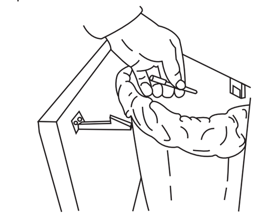

Figure 10

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

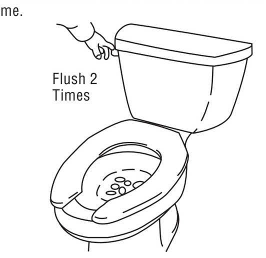

Figure 11

- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have.** OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC 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 (OTFC)?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, 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 OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

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

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

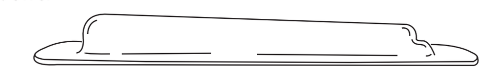

Figure 12

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

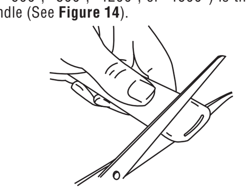

Figure 13A

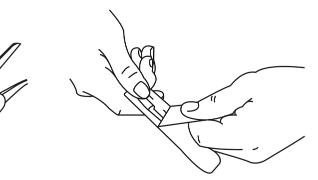

Figure 13B

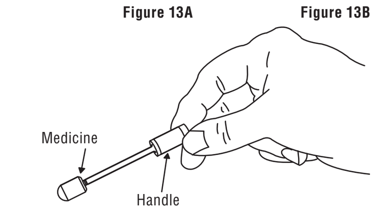

Figure 14

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

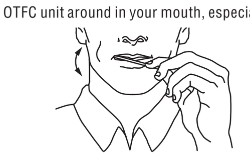

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

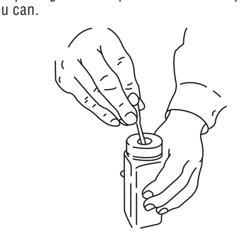

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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