

BARR LABORATORIES, INC.

Oral Transmucosal Fentanyl Citrate

MARCH 2009
1100171

R_x only

ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC)

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) (fentanyl citrate) oral transmucosal lozenge, CII
Initial U.S. Approval: 1998

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

See full prescribing information for complete boxed warning.

- **Must not be used in opioid non-tolerant patients. (1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. (5.1)**
- **Contraindicated in management of acute or postoperative pain. (4)**
- **Contains medicine in an amount that can be fatal to a child. Keep out of reach of children and discard opened units properly. (5.2)**
- **Use with strong and moderate CYP450 3A4 inhibitors may result in potentially fatal respiratory depression. (7)**

INDICATIONS AND USAGE

Oral Transmucosal Fentanyl Citrate (OTFC) is an opioid analgesic indicated only for management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. (1)

DOSAGE AND ADMINISTRATION

- 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. (1, 2)
 - Limit consumption to four or fewer units per day once successful dose is found. (2.2)
- #### DOSAGE FORMS AND STRENGTHS
- Solid drug matrix on a handle in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

1. INDICATIONS AND USAGE

2. DOSAGE AND ADMINISTRATION

- 2.1 Dose Titration
- 2.2 Dosage Adjustment
- 2.3 Administration of OTFC
- 2.4 Discontinuation of OTFC

3. DOSAGE FORMS AND STRENGTHS

4. CONTRAINDICATIONS

5. WARNINGS AND PRECAUTIONS

- 5.1 Hypoventilation (Respiratory Depression)
- 5.2 Patient/Caregiver Instructions
- 5.3 Additive CNS Depressants
- 5.4 Effects on Ability to Drive and Use Machines
- 5.5 Chronic Pulmonary Disease
- 5.6 Head Injuries and Increased Intracranial Pressure
- 5.7 Cardiac Disease
- 5.8 MAO Inhibitors

6. ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Post-Marketing 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

FULL PRESCRIBING INFORMATION:

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

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. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxycodone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

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

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

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, OTFC is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients. Patients and their caregivers must be instructed that OTFC contains a medicine in an amount which can be fatal to a child. All units must be kept out of the reach of children and opened units properly discarded [see Patient Counseling Information (17.5, 17.6), Contraindications (4) and How Supplied/Storage and Handling (16.2)].

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

1. INDICATIONS AND USAGE

Oral Transmucosal Fentanyl Citrate (OTFC) is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. 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 cancer patients and only by oncologists and pain specialists who are knowledgeable and skilled in the use of Schedule II opioids to treat cancer pain.

2. DOSAGE AND ADMINISTRATION

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 Dose Titration

Starting 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 200 mcg. Patients should be prescribed an initial 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.

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.

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

Increasing the Dose: If treatment of several consecutive breakthrough cancer pain episodes requires more than one OTFC per episode, consider an increase in dose to the next higher available strength. At each new dose of OTFC during titration, it is recommended that six units of the titration dose be prescribed. Evaluate each new dose of OTFC used in the titration period over several episodes of breakthrough cancer pain (generally 1 to 2 days) to determine whether it provides adequate efficacy with acceptable side effects. The incidence of side effects is likely to be greater during this initial titration period compared to later, after the effective dose is determined.

OTFC Titration Process

See BOXED WARNING

Start at 200 mcg
(Dispense no more than 6 units initially)

- 1 - Consume OTFC unit over 15 minutes
- 2 - Wait 15 more minutes
- 3 - If needed, consume second unit over 15 minutes
- 4 - To the OTFC dose for several episodes of breakthrough pain

Adequate relief with one unit?

Yes

Successful Dose Determined

No

Increase dose to next highest strength*
(Dispense no more than 6 units initially)

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

2.2 Dosage Adjustment

Increase the dose of OTFC when patients require more than one dosage unit per breakthrough cancer pain episode for several consecutive episodes. When titrating to an appropriate dose, prescribe small quantities (six units) at each titration step. Once a successful dose has been achieved (i.e., an average episode is treated with a single unit), limit consumption to four or fewer units per day. Consider increasing the around-the-clock opioid dose used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

2.3 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)].

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
 - Management of acute or postoperative pain. (4)
 - Intolerance or hypersensitivity to fentanyl, OTFC, or its components. (4)
- #### WARNINGS AND PRECAUTIONS
- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.1, 5.3)
 - 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") (5.2, 17.4)
 - Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1, 5.3)
 - Titrate OTFC cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to hypoventilation. (5.5, 5.7)
 - Administer OTFC with extreme caution in patients susceptible to intracranial effects of CO₂ retention. (5.6)

ADVERSE REACTIONS

Most common adverse reactions during titration phase (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache. (6.1)
Most common adverse reactions during treatment (frequency ≥5%): dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)
Dental decay has been reported. (6.2)
To report SUSPECTED ADVERSE REACTIONS, contact Barr Laboratories, Inc. at 1-800-391-5974 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Monitor patients who begin or end therapy with potent inhibitors of CYP450 3A4 for signs of opioid toxicity. (5.3, 7)

USE IN SPECIFIC POPULATIONS

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.

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 MARCH 2009

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 Overdose (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 Instruction
- 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 Unused OTFC Units When No Longer Needed
- 17.7 Medication Guide

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

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.

2.4 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 unit with the OTFC strength and the handle tag. Oral Transmucosal Fentanyl Citrate is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths [see How Supplied/Storage and Handling (16.3)].

4. CONTRAINDICATIONS

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, Oral Transmucosal Fentanyl Citrate (OTFC) is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid 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** - WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION AND POTENTIAL FOR ABUSE

5.1 Hypoventilation (Respiratory Depression)

As with all opioids, there is a risk of clinically significant hypoventilation in patients using Oral Transmucosal Fentanyl Citrate (OTFC). Accordingly, follow all patients for symptoms of respiratory depression. Hypoventilation may occur more readily when opioids are given in conjunction with other agents that depress respiration.

5.2 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. 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), and Patient Counseling Information (17.1, 17.7)].

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.

5.3 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., hypoventilation, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoenzyme (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.

5.4 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.

5.5 Chronic Pulmonary Disease

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

5.6 Head Injuries and Increased Intracranial Pressure

Administer OTFC with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ 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.

5.7 Cardiac Disease

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

5.8 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.

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 event among patients who were taking OTFC for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no adverse event to date reported 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	2	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: Hyposthesia

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: Dehydration, hypocalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

Nervous: Abnormal dreams, urinary infection, 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 12

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)].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a μ -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, cortisoll, 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 μ -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 - Warnings: Importance Of Proper Patient Selection and Potential for Abuse, Contraindications* (4), *Warnings And Precautions* (5.1), *Adverse Reactions* (6), and *Overdosage* (10)].

12.3 Pharmacokinetics

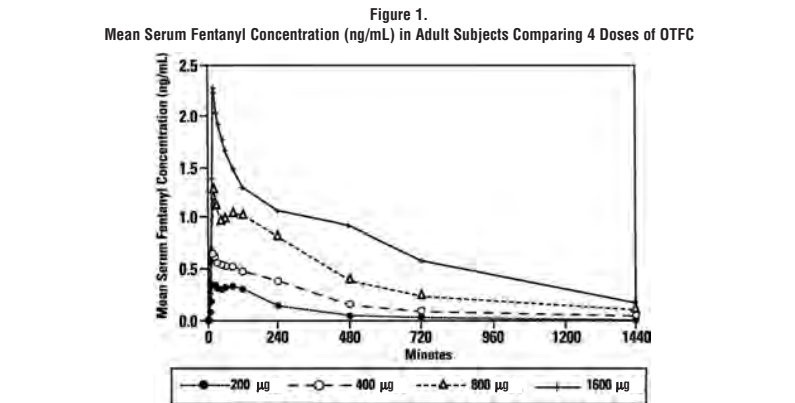
Absorption

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_{0-120} increased in a dose-dependent manner that is approximately proportional to the OTFC administered.



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 - 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 120 minutes) as measured after the start of administration.

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 albumin and 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 (V_{ss}) was 4 L/kg.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa 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 who were managed 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 with in 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.

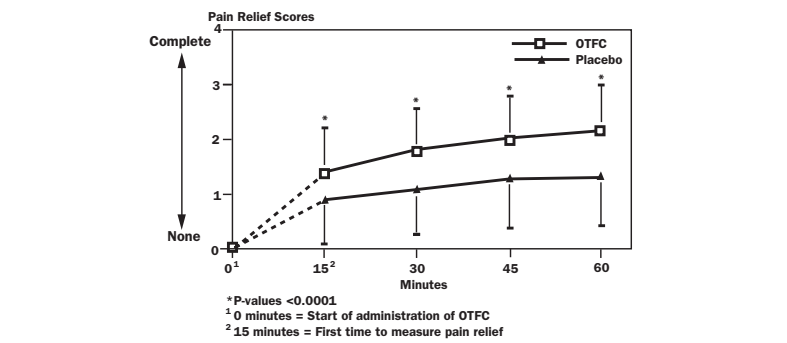
A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of OTFC for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 4.

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 $\pm$ SD	789 $\pm$ 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.

Figure 2. Pain Relief (PR) Scores (Mean $\pm$ SD) During the Double-Blind Phase - All Patients with Evaluable Episodes on Both OTFC and Placebo (N=88)



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 - Warnings: Importance Of Proper Patient Selection and Potential For Abuse, Warnings And Precautions* (5), 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 use 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 for disposal are included in the Patient Counseling Information (17.6) and in the Medication Guide (17.7). If additional assistance is required, call at 1-800-391-5962.

16.3 How Supplied

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

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) NDC 0555-0001-01
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) NDC 0555-0002-01
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) NDC 0555-0003-01
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) NDC 0555-0004-01
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) NDC 0555-0005-01
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) NDC 0555-0006-01

The dosage strength of each unit is marked on the handle tag, the blister package and the carton. See blister package and carton for product information.

Each dosage unit is individually sealed in a child-resistant, protective blister package. These blister packages are packaged 30 per shelf carton for use when patients have been titrated to the appropriate dose.

Patients should be prescribed an initial titration supply of six OTFC units. At each new dose of oral transmucosal fentanyl citrate during titration, it is recommended that only six units of the next higher dose be prescribed.

17. PATIENT COUNSELING INFORMATION

See the Medication Guide (17.7) for specific patient instructions.

17.1 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that Oral Transmucosal Fentanyl Citrate (OTFC) contains medicine in an amount that could be fatal to a child. Patients and their caregivers must be instructed 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* (5.2), and *Patient Counseling Information* (17.4)].

17.2 Dental Care

Because each OTFC unit contains approximately 2 grams of sugar (hydrated dextbrates), frequent consumption may increase the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk. Post-marketing reports of dental decay have been received in patients taking OTFC [see *Adverse Reactions* (6.2)]. In some of these patients, dental decay occurred despite 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 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. Patients and their caregivers should also have an opportunity to watch the patient safety video, which provides proper product use, storage, handling and disposal directions. Patients also have an opportunity to discuss the video with their healthcare providers. To obtain a supply of Child Safety Kits, healthcare professionals can call Barr Laboratories, Inc. at 1-800-391-5974.

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 could 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.

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 and 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 (1-800-391-5962) or seek assistance from their local DEA office.

17.7 Medication Guide

Medication Guide
Oral Transmucosal Fentanyl Citrate (OTFC)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

WARNING: You MUST keep oral transmucosal fentanyl citrate in a safe place out of the reach of children. Accidental ingestion by a child is a medical emergency and can result in death. If a child accidentally takes oral transmucosal fentanyl citrate, get emergency help right away.

Read the Medication Guide that comes with Oral Transmucosal Fentanyl Citrate before you start taking it 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 doctor about your medical condition or your treatment. Share this important information with members of your household.

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

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

- If it is used by anyone who is not already taking other opioid pain medicines and their body is not used to these medicines (not opioid tolerant)
- If it is not used exactly as prescribed.

2. Your doctor will prescribe a starting dose of OTFC that is different than other fentanyl containing medicines you may have been taking. Do not substitute OTFC for other fentanyl medicines without talking with your doctor.

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

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

OTFC is to be used only to treat breakthrough pain in adult patients with cancer (16 years of age and older) who are already taking other opioid pain medicines for their constant (around-the-clock) cancer pain. OTFC is started only after you have been taking other opioid pain medicines and your body has gotten used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.

- You must stay under your doctor's care while taking OTFC.
- OTFC must not be used for short-term pain from injuries and surgery.
- Prevent theft and misuse. Keep OTFC in a safe place to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs. Never give OTFC to anyone else, even if they have the same symptoms you have. It may harm them and even cause death. Selling or giving away this medicine is against the law.

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

Do Not Take OTFC if you:

- are not already taking other opioid pain medicines for your constant (around-the-clock) cancer pain. Never use OTFC for short-term pain from injuries or surgery or pain that will go away in a few days, such as pain from doctor or dentist visits, or any short-lasting pain.
- are allergic to anything in OTFC. The active ingredient in OTFC is fentanyl. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my doctor before I start taking Oral Transmucosal Fentanyl Citrate (OTFC)?

Tell your doctor about all of your medical and mental problems, especially the ones listed below:

- Trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- A head injury or brain problem
- Liver or kidney problems
- Seizures (convulsions or fits)
- Slow heart rate or other heart problems
- Low blood pressure
- Mental problems including major depression or hallucinations (seeing or hearing things that are not there)
- A past or present drinking problem or alcoholism, or a family history of this problem
- A past or present drug abuse or addiction problem, or a family history of this problem
- If you are diabetic. Each OTFC unit contains about 1/2 teaspoon (2 grams) of sugar.

Tell your doctor if you are:

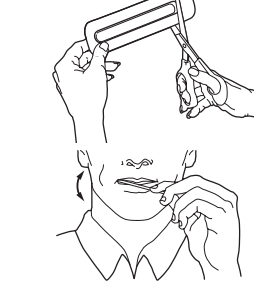
- pregnant or planning to become pregnant. OTFC may harm your unborn baby.
- breast-feeding. Fentanyl passes through your breast milk and it can cause serious harm to your baby. You should not use OTFC while breast-feeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with OTFC. Sometimes, the doses of certain medicines and OTFC need to be changed if used together. Do not take any medicine while using OTFC until you have talked to your doctor. Your doctor will tell you if it is safe to take other medicines while you are using OTFC. Be especially careful about other medicines that make you sleepy such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist.

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

- Use OTFC exactly as prescribed. Do not take OTFC more often than prescribed. Talk to your doctor about your pain. Your doctor can decide if your dose of OTFC needs to be changed.



- Each unit of OTFC is sealed in its own blister package.
- Do not open the blister package until you are ready to use OTFC.
- When you are ready to use OTFC, cut open the package using scissors and remove the OTFC unit.

- Place OTFC in your mouth between your cheeks and gums and actively suck on the medicine.
- Move OTFC around in your mouth, especially along your cheeks.
- Twist the handle often.

- 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 pain.

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.

If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth. Dispose of OTFC right away or put it in the temporary storage bottle in the Child Safety Kit for later disposal.

If you have more than 4 episodes of breakthrough cancer pain per day, talk to your doctor. The dose of OTFC may need to be adjusted.

- If you take too much OTFC or overdose, call 911 or your local emergency number for help.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) 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. Please follow these directions to dispose of the handle:

1. Once 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.
2. If any medicine remains on the handle after you have finished, place the handle under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets.
3. If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the OTFC in the temporary storage bottle that you received in the OTFC Child Safety Kit for safe keeping. Open the child-resistant cap, and place the OTFC unit completely into the bottle and close the cap tightly. Never leave unused or partially used OTFC units where children or pets can get to them.
4. Dispose of the handles in the temporary storage bottle as soon as you can by following the directions in steps 1 and 2. You must dispose of all handles in the temporary storage bottle at least once a day.

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

What should I avoid while taking Oral Transmucosal

