

FENTANYL BUCCAL- fentanyl citrate tablet

Mayne Pharma

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use fentanyl buccal tablet safely and effectively. See full prescribing information for fentanyl buccal tablet.

Fentanyl Buccal Tablet, CII
Initial U.S. Approval: 1968

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF FENTANYL BUCCAL TABLET

See full prescribing information for complete boxed warning.

- Fentanyl buccal tablet exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and reassess regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression has occurred in patients treated with fentanyl buccal tablet, including following use in opioid non-tolerant patients and improper dosing. Regularly evaluate patients, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of fentanyl buccal tablet are essential. The substitution of fentanyl buccal tablet for any other fentanyl product may result in fatal overdose. Due to the risk of fatal respiratory depression, fentanyl buccal tablet is contraindicated in opioid non-tolerant patients and in management of acute or postoperative pain, including headache/migraines. (1, 4, 5.2)
- Accidental ingestion of fentanyl buccal tablet, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (2.8, 5.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.4, 7)
- If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.8)
- Fentanyl buccal tablet is available only through a restricted program called the TIRF REMS. Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients are required to enroll in the program. Patients must be opioid tolerant to receive a TIRF medicine (5.7)
- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to fentanyl buccal tablet. (5.5)
- When dispensing, do not substitute with any other fentanyl products. (5.5)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.6, 7, 12.3)

RECENT MAJOR CHANGES

Boxed Warning	1/2024
Dosage and Administration (2.1, 2.5)	1/2024
Warnings and Precautions (5.9)	1/2024

INDICATIONS AND USAGE

Fentanyl buccal tablet is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 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)

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablet.

Limitations of Use:

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

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

- Patients must require and use around-the-clock opioids when taking fentanyl buccal tablet. (1)
- Fentanyl buccal tablet should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of fentanyl buccal tablet for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1, 5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with fentanyl buccal tablet. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with fentanyl buccal tablet. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.1, 5.2, 5.4)
- Initial dose of fentanyl buccal tablet: 100 mcg. (2.3)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablet. Limit patient access to only one strength of fentanyl buccal tablet at any one time. (2.4)
- Individually titrate to a tolerable dose that provides adequate analgesia using a single fentanyl buccal tablet. (2.5)
- No more than two doses can be taken per breakthrough pain episode. (2.3)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablet. (2.3)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed, or swallowed whole. (2.6)
- When opioid therapy is no longer required, consider discontinuing fentanyl buccal tablet along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.7)

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

Buccal Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (3)

----- **CONTRAINDICATIONS** -----

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

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue fentanyl buccal tablet if serotonin syndrome is suspected. (5.10)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly,

Cachectic, or Debilitated Patients: Regularly evaluate patients, particularly during initiation and titration. (5.11)

- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.12)
- Severe Hypotension: Regularly evaluate patients during dosage initiation and titration. Avoid use of fentanyl buccal tablet in patients with circulatory shock. (5.13)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of fentanyl buccal tablet in patients with impaired consciousness or coma. (5.14)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.19)

-----ADVERSE REACTIONS-----

Most common (frequency $\geq 10\%$): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with fentanyl buccal tablet because they may reduce analgesic effect of fentanyl buccal tablet or precipitate withdrawal symptoms. (7)

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

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Renal and Hepatic Impairment: Administer fentanyl buccal tablet with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF FENTANYL BUCCAL TABLET

Addiction, Abuse, and Misuse

Because the use of fentanyl buccal tablet exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has occurred in patients treated with fentanyl buccal tablet, including following use in opioid non-tolerant patients and improper dosing. Evaluate patients for respiratory depression, especially during initiation of fentanyl buccal tablet or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of fentanyl buccal tablet are essential. The substitution of fentanyl buccal tablet for any other fentanyl product may result in fatal overdose [see *Warnings and Precautions (5.2)*].

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

Accidental Ingestion

Accidental ingestion of even one dose of fentanyl buccal tablet, especially by children, can result in a fatal overdose of fentanyl. Death has been reported in children who have accidentally ingested fentanyl buccal tablet. Fentanyl buccal tablet must be kept out of reach of children [see *Warnings and Precautions (5.3)*].

Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of fentanyl buccal tablet and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [see *Warnings and Precautions (5.4)*, *Drug Interactions (7)*].

Risk of Medication Errors

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

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

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl buccal tablet with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Evaluate patients at frequent intervals receiving fentanyl buccal tablet and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Risk Evaluation and Mitigation Strategy (REMS)

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

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [see *Warnings and Precautions (5.8)*].

1 INDICATIONS AND USAGE

Fentanyl buccal tablet is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablet.

Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe fentanyl buccal tablet for outpatients must enroll in the TIRF REMS and comply with the requirements of the REMS to ensure safe use of fentanyl buccal tablet [see *Warnings and Precautions (5.7)*].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*]. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of fentanyl buccal tablet for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with fentanyl buccal tablet. Consider this risk when selecting an initial dose and when making dose adjustments [see *Warnings and Precautions (5)*].
- Instruct patients and caregivers to take steps to store fentanyl buccal tablet securely and to properly dispose of unused fentanyl buccal tablet as soon as no longer needed [see *Warnings and Precautions (5.1, 5.3)*].
- Fentanyl buccal tablet is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) [see *Warnings and Precautions (5.5)*].
- Fentanyl buccal tablet is NOT a generic version of any other transmucosal fentanyl product [see *Warnings and Precautions (5.5)*].

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

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with fentanyl buccal tablet [see *Warnings and*

Precautions (5.2)].

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

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see *Warnings and Precautions (5.1, 5.2, 5.4)*].

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

2.3 Initial Dosage

The initial dose of fentanyl buccal tablet is always 100 mcg with the only exception being patients already using ACTIQ.

Patients on ACTIQ

- a. For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ table below (Table 1). The doses of fentanyl buccal tablet in this table are starting doses and not intended to represent equianalgesic doses to ACTIQ. Patients must be instructed to stop the use of ACTIQ and dispose of any remaining units.

**Table 1. Initial Dosing
Recommendations for Patients on
ACTIQ**

Current ACTIQ Dose (mcg)	Initial Fentanyl Buccal Tablet Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 × 200 mcg tablets
1600	2 × 200 mcg tablets

* From this initial dose, titrate patient to effective dose.

- b. For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablet and should proceed using multiples of this tablet strength.

Repeat Dosing

- a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablet for any episode of breakthrough pain.
- b. Patients **MUST** wait at least 4 hours before treating another episode of breakthrough

pain with fentanyl buccal tablet.

2.4 Dose Titration

- a. From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablet/s over several episodes of breakthrough pain and discuss their experience with their healthcare provider to determine if a dosage adjustment is warranted.
- b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg fentanyl buccal tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
- c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablet for any breakthrough pain episode. During titration, one **dose** of fentanyl buccal tablet may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).
- d. Patients **MUST** wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablet. To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal tablet/s available at any time.
- e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely [see *How Supplied/Storage and Handling (16)*]. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.5 Maintenance Dosing

- a. Once titrated to an effective dose, patients should generally use only ONE fentanyl buccal tablet of the appropriate strength per breakthrough pain episode.
- b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode.
- c. Patients **MUST** wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablet.
- d. Dosage adjustment of fentanyl buccal tablet may be required in some patients. Generally, the fentanyl buccal tablet 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 after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage [see *Warnings and Precautions (5)*]. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.
- e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.

- f. Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue).

2.6 Administration of Fentanyl Buccal Tablet

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer fentanyl buccal tablet.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should immediately place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. Patients should not split the tablet.

The fentanyl buccal tablet should not be crushed, sucked, chewed, or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.

The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.

It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablet/s in the buccal cavity.

2.7 Discontinuation of Fentanyl Buccal Tablet

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

2.8 Disposal of Fentanyl Buccal Tablets

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279.

3 DOSAGE FORMS AND STRENGTHS

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier [see *How Supplied/Storage and Handling (16)*].

4 CONTRAINDICATIONS

Fentanyl Buccal Tablet is contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients [see *Indications and Usage (1)*, *Warnings and Precautions (5.2)*].
- Significant respiratory depression [see *Warnings and Precautions (5.2)*].
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department [see *Indications and Usage (1)*].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.11)*].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.15)*].
- Known hypersensitivity to fentanyl or components of fentanyl buccal tablet (e.g., anaphylaxis, hypersensitivity) [see *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

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

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

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl buccal tablet, and reassess all patients receiving fentanyl buccal tablet for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as fentanyl buccal tablet, but use in such patients necessitates intensive counseling about the risks and proper use of fentanyl buccal tablet along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.2)*].

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing fentanyl buccal tablet. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug. Contact local state

professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of fentanyl buccal tablet, the risk is greatest during the initiation of therapy or following a dosage increase.

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

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

Accidental ingestion of even one dose of fentanyl buccal tablet, especially by children, can result in respiratory depression and death due to an overdose of fentanyl *[see Warnings and Precautions (5.3)]*.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

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

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with fentanyl buccal tablet. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the

patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1, 5.4), *Overdosage* (10)].

5.3 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

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

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

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

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

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl buccal tablet with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

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

If concomitant use is warranted, consider prescribing naloxone for the emergency

treatment of opioid overdose [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.2)*].

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

5.5 Risk of Medication Errors

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

Fentanyl buccal tablet is not a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, do not substitute a fentanyl buccal tablet prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and fentanyl buccal tablet are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablet compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of fentanyl buccal tablet 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 except ACTIQ. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) [see *Dosage and Administration (2.1)*]. Therefore, for opioid-tolerant patients, the initial dose of fentanyl buccal tablet should always be 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects [see *Dosage and Administration (2.4)*].

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

Concomitant use of fentanyl buccal tablet with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see *Warnings and Precautions (5.2)*], particularly when an inhibitor is added after a stable dose of fentanyl buccal tablet is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl buccal tablet-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl buccal tablet with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl buccal tablet-treated patients, evaluate patients at frequent intervals and consider dosage reduction of fentanyl buccal tablet until stable drug effects are achieved [see *Drug Interactions (7)*].

Concomitant use of fentanyl buccal tablet with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid

efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl buccal tablet with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, evaluate patients at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see *Drug Interactions* (7)].

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

Because of the risk for accidental exposure, misuse, abuse, addiction, and overdose [see *Warnings and Precautions* (5.1), *Drug Abuse and Dependence* (9)], fentanyl buccal tablet is available only through a restricted program called the TIRF REMS. Under the TIRF REMS, healthcare professionals who prescribe to outpatients, the outpatients themselves, and pharmacies are required to enroll in the program.

Notable requirements of the TIRF REMS are:

- Prescribers for outpatient use must be certified with the REMS program by enrolling and completing training. Prescribers must document opioid tolerance with every fentanyl buccal tablet prescription.
- Outpatients must be enrolled in the REMS program and must be opioid-tolerant to receive fentanyl buccal tablet [see *Dosage and Administration* (2.1)].
- Outpatient pharmacies must be certified with the REMS program and verify documentation of opioid tolerance with every fentanyl buccal tablet prescription.
- Inpatient pharmacies must be certified with the REMS program and develop policies and procedures to verify opioid tolerance in inpatients who require fentanyl buccal tablet while hospitalized.
- Wholesalers and distributors must enroll in the REMS program and distribute only to certified pharmacies.

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

5.8 Neonatal Opioid Withdrawal Syndrome

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

5.9 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see *Dependence* (9.3)]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease

progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [see *Dosage and Administration* (2.7)].

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl buccal tablet with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see *Drug Interactions* (7)]. This may occur within the recommended dosage range.

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

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

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

Patients with Chronic Pulmonary Disease: fentanyl buccal tablet-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of fentanyl buccal tablet [see *Warnings and Precautions* (5.2)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Warnings and Precautions* (5.2)].

Regularly evaluate patients, particularly when initiating and titrating fentanyl buccal tablet and when fentanyl buccal tablet is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.2), *Drug Interactions* (7)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.12 Adrenal Insufficiency

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

5.13 Severe Hypotension

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

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

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), fentanyl buccal tablet may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl buccal tablet.

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

5.15 Risks of Use in Patients with Gastrointestinal Conditions

Fentanyl buccal tablet is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in fentanyl buccal tablet may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.16 Increased Risk of Seizures in Patients with Seizure Disorders

The fentanyl in fentanyl buccal tablet may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during fentanyl buccal tablet therapy.

5.17 Risks of Driving and Operating Machinery

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

5.18 Cardiac Disease

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

5.19 Application Site Reactions

Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding [see *Adverse Reactions* (6)].

6 ADVERSE REACTIONS

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

- Addiction, Abuse, and Misuse [see *Warnings and Precautions* (5.1)]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions* (5.2)]
- Interactions with Benzodiazepines and Other CNS Depressants [see *Warnings and Precautions* (5.4)]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions* (5.8)]
- Opioid-Induced Hyperalgesia and Allodynia [see *Warnings and Precautions* (5.9)]
- Serotonin Syndrome [see *Warnings and Precautions* (5.10)]
- Adrenal Insufficiency [see *Warnings and Precautions* (5.12)]
- Severe Hypotension [see *Warnings and Precautions* (5.13)]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.15)]
- Seizures [see *Warnings and Precautions* (5.16)]

6.1 Clinical Studies Experience

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

The safety of fentanyl buccal tablets has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The clinical trials of fentanyl buccal tablets were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tablets for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl

buccal tablets therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2. Adverse Events Which Occurred During Titration at a Frequency of $\geq 5\%$

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of $\geq 5\%$ within the total population that occurred after a successful dose had been determined.

Table 3. Adverse Events Which Occurred During Long-Term Treatment at a Frequency of $\geq 5\%$

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)

pain	2 (11)	1 (5)	4 (9)	7 (15)	4 (7)	10 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets. There was no evidence of excess toxicity in this subset of patients.

Application Site Reactions: In clinical trials, 10% of all patients exposed to fentanyl buccal tablets reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in $\geq 1\%$ of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment, were self-limited, and only resulted in treatment discontinuation for 2% of patients.

The duration of exposure to fentanyl buccal tablets varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the $\geq 1\%$ of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and

post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets. Events are classified by system organ class.

Adverse Events ($\geq 1\%$)

Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration

General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain

Hepatobiliary Disorders: Jaundice

Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess

Injury, Poisoning, and Procedural Complications: Fall, Spinal Compression Fracture

Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count

Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake

Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain

Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy

Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness

Renal and Urinary Disorders: Renal Failure

Respiratory, Thoracic, and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing

Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat

Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

6.2 Postmarketing Experience

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

Nervous System Disorders:

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

drugs.

- *Hyperalgesia and Allodynia*: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [see *Warnings and Precautions* (5.9)].

Endocrine Disorders:

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

- *Androgen deficiency*: Cases of androgen deficiency have occurred with use of opioids for an extended period of time [see *Clinical Pharmacology* (12.2)].

Immune System Disorders:

- *Anaphylaxis*: Anaphylaxis has been reported with ingredients contained in fentanyl buccal tablet.

General Disorders and Administration Site Conditions:

- *Drug withdrawal syndrome*

Metabolic and Nutritional Disorders:

- *Hypoglycemia*: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with fentanyl buccal tablet.

Table 4. Clinically Significant Drug Interactions with Fentanyl Buccal Tablet

Inhibitors of CYP3A4	
<i>Clinical Impact:</i>	The concomitant use of fentanyl buccal tablet and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablet is achieved [see <i>Warnings and Precautions</i> (5.6)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease [see <i>Clinical Pharmacology</i> (12.3)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of fentanyl buccal tablet/s until stable drug effects are achieved. Evaluate patients at frequent intervals for respiratory depression and sedation. If a CYP3A4 inhibitor is discontinued, consider increasing the fentanyl buccal tablet dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal.
	Macrolide antibiotics (e.g., erythromycin), azole-antifungal

<i>Examples:</i>	agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
<i>Clinical Impact:</i>	The concomitant use of fentanyl buccal tablet and CYP3A4 inducers can decrease the plasma concentration of fentanyl [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl [see <i>Warnings and Precautions (5.6)</i>]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the fentanyl buccal tablet dosage until stable drug effects are achieved. Evaluate for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl buccal tablet dosage reduction and evaluate patients at frequent intervals for signs of respiratory depression and sedation.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation). If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.1, 5.2, 5.4)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>].
<i>Intervention:</i>	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.
	Selective serotonin reuptake inhibitors (SSRIs), serotonin and

<i>Examples:</i>	norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.2)</i>].
<i>Intervention:</i>	The use of fentanyl buccal tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of fentanyl buccal tablet and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Because respiratory depression may be greater than otherwise expected, decrease the dosage of fentanyl buccal tablet and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.2, 5.4)</i>].
<i>Examples:</i>	Cyclobenzaprine, metaxalone
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Evaluate patients for signs of urinary retention or reduced gastric motility when fentanyl buccal tablet is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions (5.8)*]. Available data with fentanyl buccal tablet in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and infant associated with use of fentanyl buccal tablet for an extended period of time during pregnancy (see *Clinical Considerations*).

In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date [see *Data*].

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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

Labor or Delivery

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

Data

Human Data

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

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

Animal Data

Fentanyl (25, 50, or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses >100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

Fentanyl has been shown to be embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of fentanyl buccal tablet on a mg/m² basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of fentanyl buccal tablet based on a mg/m² basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 6 times the human dose of 800 mcg fentanyl buccal tablet per pain episode on a mg/m² basis and produced mean steady-state plasma levels that are approximately 5 times higher than the mean C_{max} observed following administration of 800 mcg dose of fentanyl buccal tablet in humans.

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100, and 400 mcg/kg). Maternal toxicity was noted at doses >100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at >100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with fentanyl buccal tablet.

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Infertility

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

8.4 Pediatric Use

The safety and efficacy of fentanyl buccal tablet have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablet in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of fentanyl buccal tablet slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression [see *Warnings and Precautions (5.11)*].

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

8.6 Patients with Renal or Hepatic Impairment

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

8.7 Sex

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

8.8 Race

The pharmacokinetic effects of race with the use of fentanyl buccal tablet have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl buccal tablet contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

Fentanyl buccal tablet contains fentanyl, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction [*see Warnings and Precautions (5.1)*].

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of fentanyl buccal tablet increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of fentanyl buccal tablet with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of fentanyl buccal tablet abuse include those with a history of prolonged use of any opioid, including products containing fentanyl, those with a history of drug or alcohol abuse, or those

who use fentanyl buccal tablet in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Fentanyl buccal tablet, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Fentanyl Buccal Tablet

Abuse of fentanyl buccal tablet poses a risk of overdose and death. The risk is increased with concurrent use of fentanyl buccal tablet with alcohol and/or other CNS depressants.

Fentanyl buccal tablet is approved for oral transmucosal use only.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

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

10 OVERDOSAGE

Clinical Presentation

Acute overdose with fentanyl can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see *Clinical Pharmacology* (12.2)].

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

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

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

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

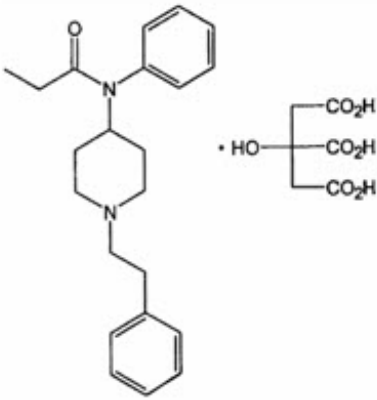
11 DESCRIPTION

Fentanyl buccal tablet is an opioid agonist, intended for buccal mucosal administration.

Fentanyl buccal tablet is designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

Fentanyl buccal tablet employs the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Effects on the Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu* opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and to electrical stimulation.

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or

syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [see *Adverse Reactions* (6.2)]. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

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

Effects on the Immune System

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

Concentration-Efficacy Relationships

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

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals [see *Dosage and Administration* (2.1)].

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [see *Dosage and Administration* (2.1, 2.5)].

Concentration-Adverse Reaction Relationships

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

Respiratory System

All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration [see *Warnings and Precautions* (5), *Overdosage* (10)].

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of fentanyl buccal tablet increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption

Following buccal administration of fentanyl buccal tablet, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of fentanyl buccal tablet is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablet and ACTIQ (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablet) (Table 5).

Table 5. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablet or ACTIQ

Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablet 400 mcg	ACTIQ 400 mcg (adjusted dose)[†]
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)[‡]	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
AUC_{0-tmax} (ng·hr/mL)	0.40 ± 0.18	0.14 ± 0.05
AUC_{0-inf} (ng·hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.

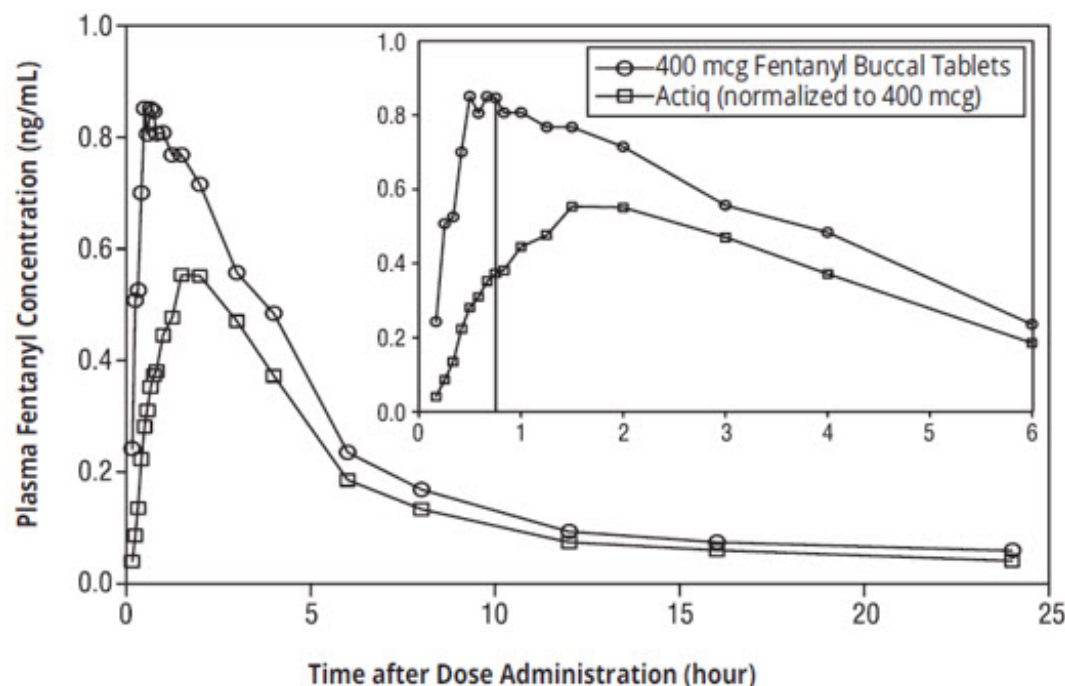
[†] ACTIQ data was dose adjusted (800 mcg to 400 mcg).

[‡] Data for T_{max} presented as median (range).

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablet was also greater (approximately 50%) compared to ACTIQ.

Due to differences in drug delivery, measures of exposure (C_{max} , $AUC_{0-t_{max}}$, AUC_{0-inf}) associated with a given dose of fentanyl were substantially greater with fentanyl buccal tablet compared to ACTIQ (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.5)]. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablet.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablet and ACTIQ in Healthy Subjects



ACTIQ data was dose adjusted (800 mcg to 400 mcg).

Mean pharmacokinetic parameters are presented in Table 6. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 6. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

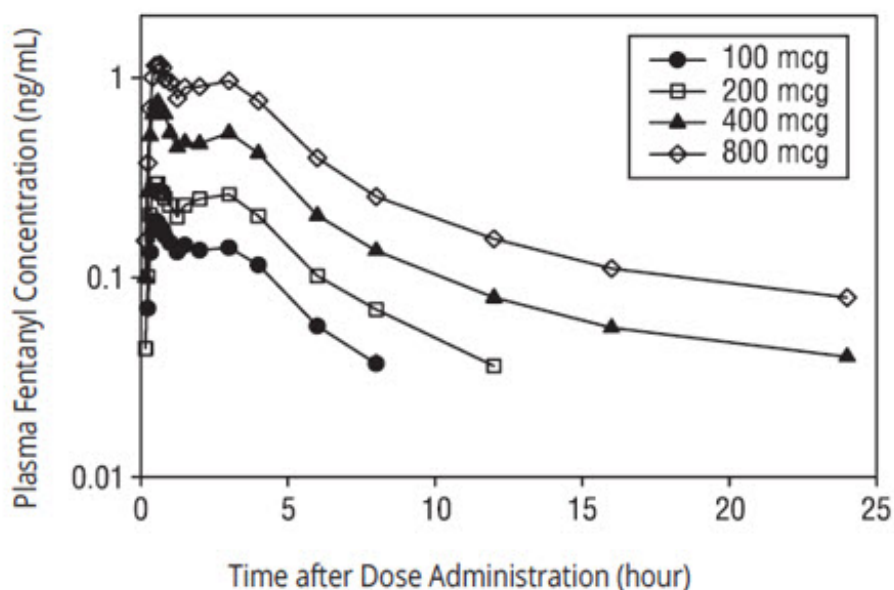
Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90
T_{max} , minute† (range)	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
AUC_{0-inf} (ng·hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0-t_{max}}$ (ng·hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
	2.63	4.43	11.09	11.70

$T_{1/2}$, hr†	(1.47 - 13.57)	(1.85 - 20.76)	(4.63 - 20.59)	(4.63 - 28.63)
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* Based on venous sampling.

† Data for T_{max} presented as median (range).

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablet was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 7.

Table 7. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	AUC_{0-tmax} (ng·hr/mL)	AUC_{0-8} (ng·hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement.

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (V_{ss}/F) was 25.4 L/kg.

Elimination

Metabolism

The metabolic pathways following buccal administration of fentanyl buccal tablet have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active [see *Drug Interactions (7)*].

Excretion

Disposition of fentanyl following buccal administration of fentanyl buccal tablet has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Sex

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2.3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was

observed.

Mutagenesis

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

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 8.6 times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

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

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablet was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid-tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablet. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablet and 3 being placebo. Patients used one tablet of study drug (either fentanyl buccal tablet or placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45, and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline (SPID₃₀) was the primary efficacy measure.

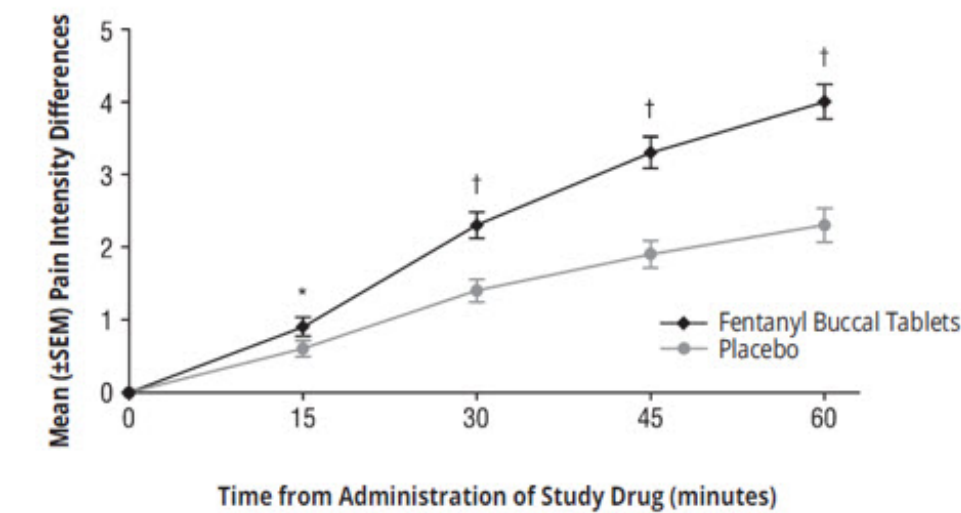
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 8. The median dose was 400 mcg.

Table 8. Successful Dose of Fentanyl Buccal Tablet Following Initial Titration

Fentanyl Buccal Tablet Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)


The LS mean (SE) SPID₃₀ for fentanyl buccal tablet-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl buccal tablets are supplied in individually sealed, child-resistant blister packages. Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with , and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
			NDC 51862

100 mcg	1	Blue	NDC 51862-634-28
200 mcg	2	Orange	NDC 51862-635-28
400 mcg	4	Sage green	NDC 51862-636-28
600 mcg	6	Magenta (pink)	NDC 51862-637-28
800 mcg	8	Yellow	NDC 51862-638-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F to 86°F) until ready to use. (See USP Controlled Room Temperature.)

Protect fentanyl buccal tablet from freezing and moisture. Do not use if the blister package has been tampered with.

Store fentanyl buccal tablet securely and dispose of properly.

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal of Unused and Used Fentanyl Buccal Tablets [see Medication Guide / Instructions for Use].

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store fentanyl buccal tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving fentanyl buccal tablets unsecured can pose a deadly risk to others in the home [see *Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)*].

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused fentanyl buccal tablets should be disposed of by removing fentanyl buccal tablets from the blister cards and flushing the unused medication down the toilet (if a drug take-back option is not readily available). Do not flush the fentanyl buccal tablet blister packages or cartons down the toilet. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Disposal of Unopened Fentanyl Buccal Tablet Blister Packages When No Longer Needed:

- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablet are provided in the Fentanyl Buccal Tablet Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to

call the Teva Pharmaceuticals toll-free number (1-888-483-8279) or seek assistance from their local DEA office.

Addiction, Abuse, and Misuse

Inform patients that the use of fentanyl buccal tablet, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions* (5.1)]. Instruct patients not to share fentanyl buccal tablet with others and to take steps to protect fentanyl buccal tablet from theft or misuse.

Life-Threatening Respiratory Depression

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see *Warnings and Precautions* (5.2)].

Accidental Ingestion

- Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure [see *Warnings and Precautions* (5.3)].
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions* (5.3)].
- Instruct patients to take steps to store fentanyl buccal tablet securely and to dispose of unused fentanyl buccal tablet [see *Dosage and Administration* (2.8), *Warnings and Precautions* (5.3, 5.7)].
- Instruct patients and caregivers to keep both used and unused fentanyl buccal tablet out of the reach of children [see *Warnings and Precautions* (5.3)].

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)

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

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with fentanyl buccal tablet. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program) [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.2)].

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

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or

suspected opioid overdose, even if naloxone is administered [*see Overdosage (10)*].

If naloxone is prescribed, also advise patients and caregivers:

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

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

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

- Outpatients must be enrolled in the REMS program
- Patients must be opioid-tolerant to receive fentanyl buccal tablet.

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

Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients are required to enroll in the program. Inpatient pharmacies must develop policies and procedures to verify opioid tolerance in inpatients who require fentanyl buccal tablet while hospitalized [*see Warnings and Precautions (5.7)*].

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain [*see Warnings and Precautions (5.9), Adverse Reactions (6.2)*].

Serotonin Syndrome

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

MAOI Interaction

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

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

- Instruct patients not to take fentanyl buccal tablet 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 fentanyl buccal tablet 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 fentanyl buccal tablet.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLET USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablet for any breakthrough pain episode.
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablet.
- Instruct patients NOT to share fentanyl buccal tablet and that sharing fentanyl buccal tablet with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablet contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablet and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.
- Instruct patients that fentanyl buccal tablet is not to be swallowed whole; this will reduce the effectiveness of the medication. The tablet is to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their healthcare provider if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablet.
- Instruct patients to use fentanyl buccal tablet exactly as prescribed by their healthcare provider and not to take fentanyl buccal tablet more often than prescribed.
- Provide patients and their caregivers with a Medication Guide each time fentanyl buccal tablet is dispensed because new information may be available.

Driving or Operating Heavy Machinery

Inform patients that fentanyl buccal tablet may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions (5.17)*].

Constipation

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

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms

and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.12)]*.

Hypotension

Inform patients that fentanyl buccal tablet may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.13)]*.

Anaphylaxis

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

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that use of fentanyl buccal tablet for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that fentanyl buccal tablet can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Lactation

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

Infertility

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

Dispense with Medication Guide available at: products.maynepharma.com

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Medication Guide

Fentanyl Buccal Tablet, CII

IMPORTANT:

Do not use fentanyl buccal tablet 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 fentanyl buccal tablets in a safe place away from children.

Get emergency medical help right away if:

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

These are medical emergencies that can cause death. If possible, try to remove fentanyl buccal tablet from the mouth.

Fentanyl buccal tablet is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. Fentanyl buccal tablet 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 fentanyl buccal tablet if you are not opioid tolerant.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablet:

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

- Fentanyl buccal tablets are only available at pharmacies that are part of the TIRF REMS. Your healthcare provider can help you locate a pharmacy closest to your home where you can have your fentanyl buccal tablet prescription filled.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take fentanyl buccal tablet if:

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

Before taking fentanyl buccal tablet, tell your healthcare provider if you have a history of:

- troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems

Tell your healthcare provider if you are:

- **noticing your pain getting worse.** If your pain gets worse after you take fentanyl buccal tablet, do not take more fentanyl buccal tablet without first talking to your healthcare provider. Talk to your healthcare provider if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking fentanyl buccal tablet.
- **pregnant or planning to become pregnant.** Use of fentanyl buccal tablet for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl passes into breast milk and may harm your baby. Carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Seek immediate medical care if you notice these signs.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablet with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablet:

- Do not change your dose. Take fentanyl buccal tablet exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Instructions for Use at the end of this Medication Guide for information about how to use fentanyl buccal tablet.**
- **Use fentanyl buccal tablet whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablet, or swallow the tablet whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using fentanyl buccal tablet. If there is any of the fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- You must not use more than 2 doses of fentanyl buccal tablet for each episode of breakthrough cancer pain.
- Use **1** dose of fentanyl buccal tablet for an episode of breakthrough cancer pain.
- If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of fentanyl buccal tablet, you can use **only 1** more dose of fentanyl buccal tablet as instructed by your healthcare provider.
- If your breakthrough pain does not get better after the second dose of fentanyl buccal tablet, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tablet at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tablet.
- If you only need to take 1 dose of fentanyl buccal tablet for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of fentanyl buccal tablet for a **new** episode of breakthrough pain.
- If you need to use 2 doses of fentanyl buccal tablet for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tablet for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using fentanyl buccal tablets.
- Talk to your healthcare provider if your dose of fentanyl buccal tablets does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tablets 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 the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.
- Do not stop taking fentanyl buccal tablets without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- After you stop taking, or when fentanyl buccal tablet is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed?**" for proper disposal of fentanyl buccal tablets.

- Dispose of expired, unwanted, or unused fentanyl buccal tablets by removing the product from the blister cards and promptly flushing down the toilet (if a drug take-back option is not readily available.) Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.
- **DO NOT** Drive or operate heavy machinery until you know how fentanyl buccal tablet affects you. Fentanyl buccal tablet can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablet may cause you to overdose and die.
- **DO NOT Switch from fentanyl buccal tablet to other medicines that contain fentanyl without talking to your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tablet is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of fentanyl buccal tablet that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of fentanyl buccal tablet:

- Constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs, and feet. Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- Pain, irritation, or sores at the application site (on your gum, on the inside of your cheek, or under your tongue). Tell your healthcare provider if this is a problem for you.

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

- Trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablet 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 take any more fentanyl buccal tablet until you have talked to your healthcare provider.**

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

How should I store fentanyl buccal tablets?

- **Always keep fentanyl buccal tablets in a safe place away from children and from anyone for whom it has not been prescribed. Protect fentanyl buccal tablets from theft.**
- **Store fentanyl buccal tablets at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use. Do not freeze fentanyl buccal tablets.**
- **Keep fentanyl buccal tablets in the original blister unit. Do not remove**

Keep fentanyl buccal tablets from its blister packaging for storage in a temporary container, such as a pill box.

- **Keep fentanyl buccal tablets dry.**

How should I dispose of unused fentanyl buccal tablets when they are no longer needed?

- **Dispose of any unused fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.**
 - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units, or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 or call your local Drug Enforcement Agency (DEA) office.**

General information about fentanyl buccal tablet

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

This Medication Guide summarizes the most important information about fentanyl buccal tablet. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about fentanyl buccal tablet that is written for health 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 in fentanyl buccal tablet?

Active Ingredient: fentanyl citrate

Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient Instructions for Use

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

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

- **Fentanyl buccal tablets come packaged as a blister card containing 4 blister units. Each blister unit contains 1 fentanyl buccal tablet. Do not**

open a blister until ready to use.

- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as

XXX mcg

(See Figure 1).

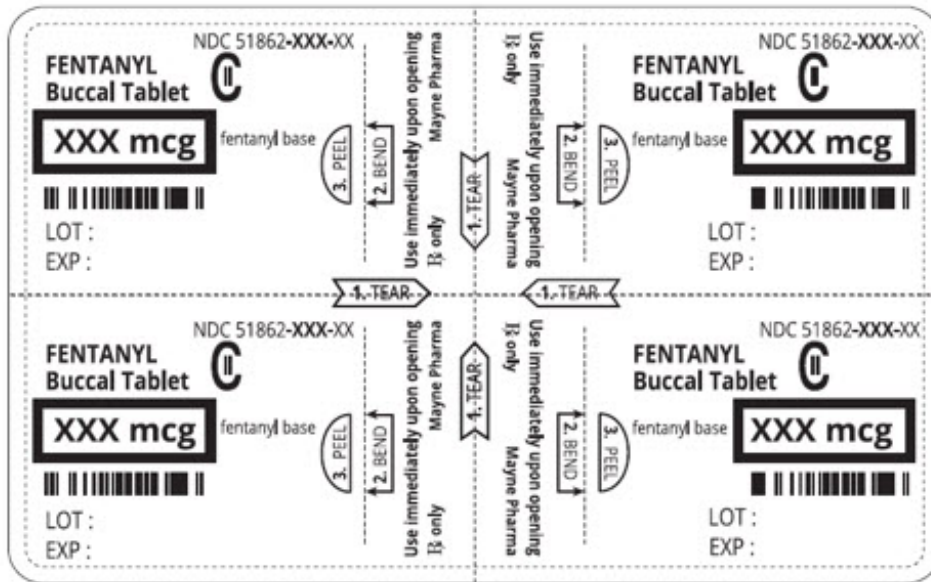


Figure 1

- Peel back foil on blister unit to expose tablet (See Figure 2).



Figure 2

- Do not push the tablet through the foil on the blister unit because this could damage the tablet.
- When removed from the blister unit, fentanyl buccal tablet must be used right away.
- Use fentanyl buccal tablet whole.
- Do not crush, split, suck, or chew fentanyl buccal tablet, or swallow the tablet whole. You will get less relief for your breakthrough cancer pain.
- You can place a fentanyl buccal tablet:
 - in your mouth above a rear molar tooth between the upper cheek and gum (See Figure 3). Switch (alternate) sides of your mouth for each

dose.



Figure 3

OR,

- **on the floor of your mouth, under your tongue (See Figures 4a, 4b, 4c, 4d).**
 - **When placing the tablet under your tongue, first lift your tongue (4b), then place the tablet under your tongue (4c), and lower your tongue over the tablet (4d).**



Figure 4a Figure 4b Figure 4c Figure 4d

- **Leave the tablet in place until it dissolves. A fentanyl buccal tablet generally takes between 14 to 25 minutes to dissolve.**
- **After 30 minutes, if there is any fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.**
- **If you cannot use fentanyl buccal tablet in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do.**

Distributed by:
Mayne Pharma
Raleigh, NC 27609
Printed in USA

call 1-844-825-8500

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

Revised: 01/2024

PRINCIPAL DISPLAY PANEL - 100 mcg Tablet Blister Pack Carton

NDC 51862-634-28

FENTANYL Buccal Tablets CII

Equivalent to 100 mcg fentanyl base

28 Buccal Tablets (4 tablets x 7 cards)

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

WARNING: Keep out of the reach of children

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY

DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.

Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

Distributed by:

Mayne Pharma

Raleigh, NC 27609

mayne pharma

IMPORTANT:
Fentanyl Buccal Tablets are available only through a restricted program called the TIRF REMS Access program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

FENTANYL Buccal Tablets

28 Buccal Tablets (4 tablets x 7 cards)

! WARNING: Keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS
 Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

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Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

Distributed by:
Mayne Pharma
Raleigh, NC 27609

Information for Pharmacist:

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- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

NDC 51862-634-28

FENTANYL Buccal Tablets 

Equivalent to **100 mcg** fentanyl base

Each tablet contains fentanyl citrate equivalent to 100 mcg fentanyl base.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

Usual Dosage: See package insert.
Print Medication Guides at:
products.maynepharma.com

Rx Only
28 Buccal Tablets



For information about this product call: 1-888-483-8279
Rev. 1/2023
400-30-100160.04
Rx Only
28 Buccal Tablets (4 tablets x 7 cards)

Equivalent to 100 mcg fentanyl base

FENTANYL Buccal Tablets

NDC 51862-634-28

28 Buccal Tablets (4 tablets x 7 cards)
 Rx Only

Do NOT split, crush, suck, chew, or swallow Tablet.
For Buccal or Sublingual Administration.
Safe use of this product requires that the patient
and/or caregiver read the enclosed Medication
Guide for important warnings and directions.

9 8 2 - 4 5 9 - 2 9 8 1 5 5

GTIN 00351862634286

**WARNING: keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS
Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed**

Equivalent to 100 mcg fentanyl base

FENTANYL Buccal Tablets

NDC 51862-634-28

Non-Varnish Area

Serialization Coding Area

Non-Varnish Area

400-30-100160-04

Non-Varnish Area

FENTANYL Buccal Tablets CII

Equivalent to 200 mcg fentanyl base

28 Buccal Tablets (4 tablets x 7 cards)

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

WARNING: Keep out of the reach of children

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY

DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.

Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

Distributed by:

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IMPORTANT:
Fentanyl Buccal Tablets are available only through a restricted program called the TIRF REMS Access program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

FENTANYL Buccal Tablets

28 Buccal Tablets (4 tablets x 7 cards)

WARNING: Keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS
 Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.
Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

Distributed by:
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Raleigh, NC 27609

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

NDC 51862-635-28

FENTANYL Buccal Tablets (II)

Equivalent to **200 mcg** fentanyl base

Each tablet contains fentanyl citrate equivalent to 200 mcg fentanyl base.

Store at 20°-25°C (68°-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. (See USP Controlled Room Temperature.)

Usual Dosage: See package insert.

Print Medication Guides at:
products.maynepharm.com

Rx Only
28 Buccal Tablets

Equivalent to 200 mcg fentanyl base

FENTANYL Buccal Tablets

NDC 51862-635-28

Rx Only
28 Buccal Tablets (4 tablets x 7 cards)

WARNING: Keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS
 Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

Equivalent to 200 mcg fentanyl base

FENTANYL Buccal Tablets

NDC 51862-635-28

Non-Varnish Area

FENTANYL Buccal Tablets CII

Equivalent to 400 mcg fentanyl base

28 Buccal Tablets (4 tablets x 7 cards)

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

WARNING: Keep out of the reach of children

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY

DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.

Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

Distributed by:

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Raleigh, NC 27609

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Place pharmacy label here.

IMPORTANT:
Fentanyl Buccal Tablets are available **only** through a restricted program called the TIRF REMS Access program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

Fentanyl Buccal Tablets are available only through a restricted program called the TIRF REMS Access program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

Rx Only
28 Buccal Tablets

The diagram illustrates a 1D barcode structure. It features a horizontal bar at the top, divided into two sections. The left section is labeled "Serialization Coding Area" and contains a series of vertical bars of varying heights, representing a barcode. The right section is a solid black rectangle. Below the horizontal bar, there is a large, empty rectangular area, likely representing the data area of the barcode.

NDC 51862-636-28

FENTANYL Buccal Tablets
NDC 51862-636-28

Equivalent to 400 mcg fentanyl base

WARNING: Keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOD THERAPY
DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.
Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication guide for important warnings and directions.
Rx Only

28 Buccal Tablets (4 tablets x 7 cards)

NDC 51862-636-28

FENTANYL Buccal Tablets
NDC 51862-636-28

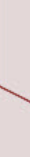
Equivalent to 400 mcg fentanyl base

For information about this product call: 1-888-483-8279
Rev. 1/2023
400-30-100162.04
Rx Only

28 Buccal Tablets (4 tablets x 7 cards)

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A diagram of a rectangular panel, likely representing a piece of wood or a composite material. The panel is light gray with a thin black border. In the center, there is a smaller, slightly offset rectangular area labeled "Non-Varnish Area" in bold black text. This central area is also light gray but appears to be a different material or finish, as it is not varnished. The panel is shown at a slight angle, giving it a three-dimensional appearance.



The diagram shows a rectangular label with a white background and a black border. A large, irregular black shape is positioned in the upper right corner, representing a non-varnish area. To the left of this shape, the text "Non-Varnish Area" is printed in a bold, black, sans-serif font. Below the text, the number "400-30-100162-06" is printed in a smaller, black, sans-serif font. A barcode is located to the right of the text and number, consisting of vertical black bars of varying widths.

FENTANYL Buccal Tablets CII

Equivalent to 600 mcg fentanyl base

28 Buccal Tablets (4 tablets x 7 cards)

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

WARNING: Keep out of the reach of children

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY

DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.

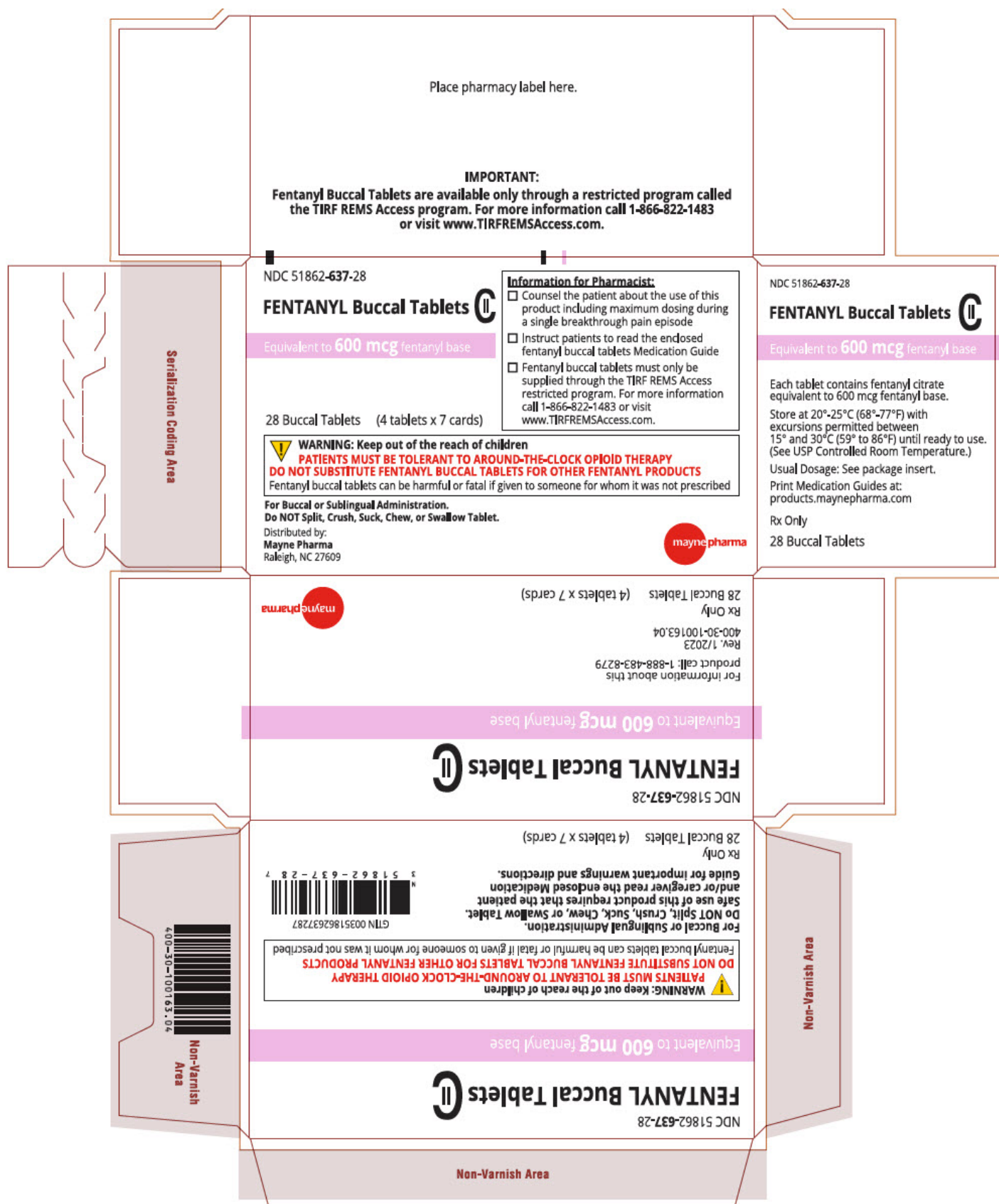
Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

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PRINCIPAL DISPLAY PANEL - 800 mcg Tablet Blister Pack Carton

NDC 51862-638-28

FENTANYL Buccal Tablets CII

Equivalent to 800 mcg fentanyl base

28 Buccal Tablets (4 tablets x 7 cards)

Information for Pharmacist:

- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Instruct patients to read the enclosed fentanyl buccal tablets Medication Guide
- ☐ Fentanyl buccal tablets must only be supplied through the TIRF REMS Access restricted program. For more information call 1-866-822-1483 or visit www.TIRFREMSAccess.com.

WARNING: Keep out of the reach of children

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY

DO NOT SUBSTITUTE FENTANYL BUCCAL TABLETS FOR OTHER FENTANYL PRODUCTS

Fentanyl buccal tablets can be harmful or fatal if given to someone for whom it was not prescribed

For Buccal or Sublingual Administration.

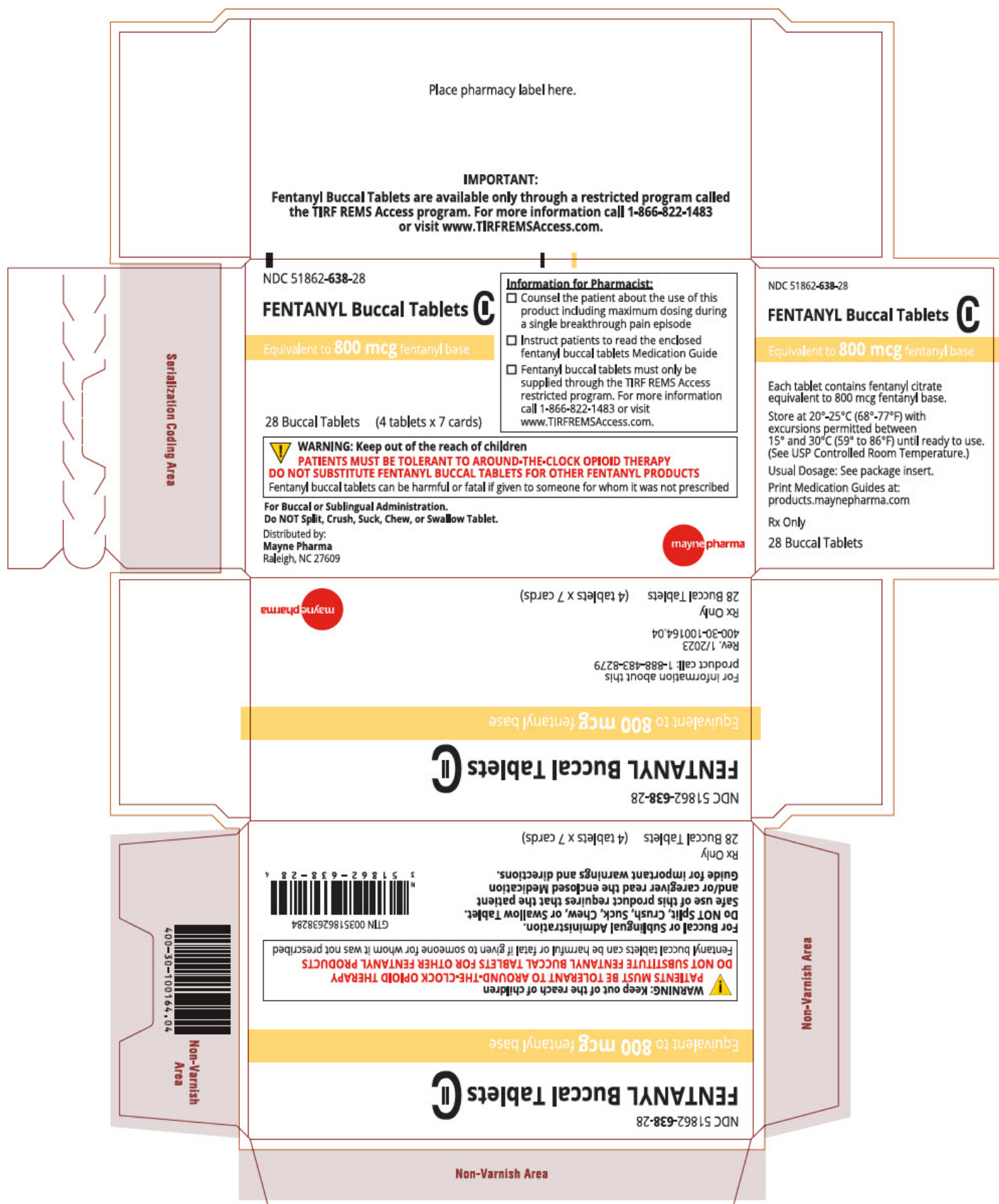
Do NOT Split, Crush, Suck, Chew, or Swallow Tablet.

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FENTANYL BUCCAL

fentanyl citrate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-634	
Route of Administration	BUCCAL, SUBLINGUAL	DEA Schedule	CII	
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
Fentanyl Citrate (UNII: MUN5LYG46H) (Fentanyl - UNII:UF599785JZ)		Fentanyl	100 ug	
Inactive Ingredients				
Ingredient Name			Strength	
Mannitol (UNII: 3OWL53L36A)				
Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2)				
Sodium Bicarbonate (UNII: 8MDF5V39QO)				
Sodium Carbonate (UNII: 45P3261C7T)				
Anhydrous Citric Acid (UNII: XF417D3PSL)				
Magnesium Stearate (UNII: 70097M6I30)				
Product Characteristics				
Color	WHITE	Score	no score	
Shape	ROUND	Size	6mm	
Flavor		Imprint Code	1;C	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-634-28	28 in 1 CARTON	06/14/2019	11/30/2024
1	NDC:51862-634-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021947		06/14/2019	11/30/2024

FENTANYL BUCCAL

fentanyl citrate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-635

Route of Administration		BUCCAL, SUBLINGUAL		DEA Schedule		CII	
Active Ingredient/Active Moiety							
Ingredient Name				Basis of Strength		Strength	
Fentanyl Citrate (UNII: MUN5LYG46H) (Fentanyl - UNII:UF599785JZ)				Fentanyl		200 ug	
Inactive Ingredients							
Ingredient Name						Strength	
Mannitol (UNII: 3OWL53L36A)							
Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2)							
Sodium Bicarbonate (UNII: 8MDF5V39QO)							
Sodium Carbonate (UNII: 45P3261C7T)							
Anhydrous Citric Acid (UNII: XF417D3PSL)							
Magnesium Stearate (UNII: 70097M6I3O)							
Product Characteristics							
Color		WHITE	Score		no score		
Shape		ROUND	Size		8mm		
Flavor			Imprint Code		2;C		
Contains							
Packaging							
#	Item Code	Package Description		Marketing Start Date		Marketing End Date	
1	NDC:51862-635-28	28 in 1 CARTON		06/14/2019		01/31/2025	
1	NDC:51862-635-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product					
Marketing Information							
Marketing Category		Application Number or Monograph Citation		Marketing Start Date		Marketing End Date	
NDA authorized generic		NDA021947		06/14/2019		01/31/2025	

FENTANYL BUCCAL			
fentanyl citrate tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-636
Route of Administration	BUCCAL, SUBLINGUAL	DEA Schedule	CII

Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
Fentanyl Citrate (UNII: MUN5LYG46H) (Fentanyl - UNII:UF599785JZ)			Fentanyl	400 ug
Inactive Ingredients				
Ingredient Name				Strength
Mannitol (UNII: 3OWL53L36A)				
Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2)				
Sodium Bicarbonate (UNII: 8MDF5V39QO)				
Sodium Carbonate (UNII: 45P3261C7T)				
Anhydrous Citric Acid (UNII: XF417D3PSL)				
Magnesium Stearate (UNII: 70097M6I30)				
Product Characteristics				
Color	WHITE	Score	no score	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	4;C	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-636-28	28 in 1 CARTON	06/14/2019	01/31/2026
1	NDC:51862-636-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic		NDA021947	06/14/2019	01/31/2026

FENTANYL BUCCAL			
fentanyl citrate tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-637
Route of Administration	BUCCAL, SUBLINGUAL	DEA Schedule	CII
Active Ingredient/Active Moiety			

Ingredient Name			Basis of Strength	Strength
Fentanyl Citrate (UNII: MUN5LYG46H) (Fentanyl - UNII:UF599785JZ)			Fentanyl	600 ug
Inactive Ingredients				
Ingredient Name			Strength	
Mannitol (UNII: 3OWL53L36A)				
Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2)				
Sodium Bicarbonate (UNII: 8MDF5V39QO)				
Sodium Carbonate (UNII: 45P3261C7T)				
Anhydrous Citric Acid (UNII: XF417D3PSL)				
Magnesium Stearate (UNII: 70097M6I30)				
Product Characteristics				
Color	WHITE	Score	no score	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	6;C	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-637-28	28 in 1 CARTON	06/14/2019	01/31/2026
1	NDC:51862-637-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic		NDA021947	06/14/2019	01/31/2026

FENTANYL BUCCAL			
fentanyl citrate tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-638
Route of Administration	BUCCAL, SUBLINGUAL	DEA Schedule	CII
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength

Fentanyl Citrate (UNII: MUN5LYG46H) (Fentanyl - UNII:UF599785JZ)			Fentanyl	800 ug
Inactive Ingredients				
Ingredient Name				Strength
Mannitol (UNII: 3OWL53L36A)				
Sodium Starch Glycolate Type A Potato (UNII: 5856J3G2A2)				
Sodium Bicarbonate (UNII: 8MDF5V39QO)				
Sodium Carbonate (UNII: 45P3261C7T)				
Anhydrous Citric Acid (UNII: XF417D3PSL)				
Magnesium Stearate (UNII: 70097M6I30)				
Product Characteristics				
Color	WHITE	Score	no score	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	8;C	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-638-28	28 in 1 CARTON	06/14/2019	01/31/2026
1	NDC:51862-638-01	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
NDA authorized generic	NDA021947		06/14/2019	01/31/2026

Labeler - Mayne Pharma (867220261)

Revised: 2/2024

Mayne Pharma