Use the lowest effective dosage for the shortest duration consistent with individual patient needs.

- Patients must require and use around-the-clock opioids while taking FENTORA. (1)

As a part of the TIRF REMS, FENTORA may be dispensed by outpatient pharmacies only to patients enrolled in the program (5.7). For inpatient administration of FENTORA, patient and pharmacist education is required to ensure proper administration of the drug.

- Concomitant use with benzodiazepines or other CNS depressants; risk of medication errors; addiction, abuse, and misuse; and neonatal opioid withdrawal syndrome.

See full prescribing information for complete boxed warning.

• Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, FENTORA is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (5.1)

• Accidental ingestion of FENTORA, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5.2)

• Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.2)

• Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)

• When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to FENTORA. (5.5)

• When dispensing, do not substitute with any other fentanyl products. (5.5)

• FENTORA is available only through a restricted program called the TIRF REMS. Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

• Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

• Discuss availability of naloxone with the patient and caregiver and assess each patient’s need for access to naloxone, both when initiating and renewing treatment with FENTORA. Consider prescribing naloxone based on the patient’s risk factors for overdose. (2.2, 5.1, 5.4, 5.6)

• Initial dose of FENTORA: 100 mcg (5.3)

• Initiate titration using multiples of 100 mcg FENTORA tablet. Limit patient access to only one strength of FENTORA at any one time. (2.4)

• Individually titrate to a tolerable dose that provides adequate analgesia using single FENTORA 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 FENTORA. (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 FENTORA along with a gradual downward of other opioid to minimize 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 the absence of resuscitative equipment. (4)

• Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)

• Known hypersensitivity to fentanyl or components of FENTORA. (4)

- WARNINGS AND PRECAUTIONS

• Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients. (4)

• Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue FENTORA if serotonin syndrome is suspected. (5.10)

• Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.1)

• Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of FENTORA in patients with circulatory shock. (5.12)

• Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of FENTORA in patients with impaired consciousness or coma. (5.13)

• Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.18)

- ADVERSE REACTIONS

Most common (frequency ≥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/Agonist and Partial Agonist Opioid Analgesics: Avoid use with FENTORA because they may reduce analgesic effect of FENTORA 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 FENTORA with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.2)

- 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 FENTORA. Consider prescribing naloxone based on the patient’s risk factors for overdose. (2.2, 5.1, 5.4, 5.6)

- Initial dose of FENTORA: 100 mcg (5.3)

- Initiate titration using multiples of 100 mcg FENTORA tablet. Limit patient access to only one strength of FENTORA at any one time. (2.4)

- Individually titrate to a tolerable dose that provides adequate analgesia using single FENTORA 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 FENTORA. (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 FENTORA along with a gradual downward of other opioid to minimize withdrawal effects. (2.7)
FENTORA® (fentanyl buccal tablet), CII

1 INDICATIONS AND USAGE
FENTORA 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 per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydrocodone 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 FENTORA.

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 in opioid non-tolerant patients [see Contraindications (4)].
- Accidental Ingestion

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

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. FENTORA must be kept out of reach of children [see Warnings and Precautions (5.2)].

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage and Administration Instructions
- Healthcare professionals who prescribe FENTORA for outpatients must enroll in the TIRF REMS and comply with the requirements of the REMS to ensure safe use of FENTORA [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 (5.6)].
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient’s severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.6)].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with FENTORA and adjust the dosage accordingly [see Warnings and Precautions (5.7)].
- Instruct patients and caregivers to take steps to store FENTORA securely and to properly dispose of unused FENTORA as soon as no longer needed [see Warnings and Precautions (5.4, 5.6)].
- FENTORA 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)].
- FENTORA 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 FENTORA [see Warnings and Precautions (5.1), Patient Counseling Information (17)].

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

Consider prescribing naloxone, based on the patient’s risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see Warnings and Precautions (5.1, 5.4, 5.6)].

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

2.3 Initial Dosage
The initial dose of FENTORA is always 100 mcg with the only exception being patients already receiving and who are tolerant to around-the-clock opioid therapy who are transitioning to FENTORA. 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 FENTORA 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.
It is recommended that patients alternate sides of the mouth when administering subsequent doses of FENTORA in the buccal cavity.

*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 FENTORA 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 FENTORA for any episode of breakthrough pain.

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

### 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 FENTORA 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 place 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 FENTORA tablet doses for 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 FENTORA for any breakthrough pain episode. During titration, one dose of FENTORA 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 FENTORA. To reduce the risk of overdose during titration, patients should have only one strength of FENTORA tablets available at any time.

e. Patients should be strongly encouraged to use all of their FENTORA tablets of one strength prior to being prescribed the next strength. If this is not practical, unused FENTORA should be disposed of safely (see How Supplied/Storage and Handling [6]). Dispose of any unopened FENTORA 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 FENTORA 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 FENTORA.

d. Dosage adjustment of FENTORA may be required in some patients. Generally, the FENTORA 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.

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 FENTORA

**Opening the Blister Package**

1. Instruct patients not to open the blister until ready to administer FENTORA.
2. Separate the blister from the blister unit 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 FENTORA tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire tablet on the buccal pouch of the cheek (if the patient has been instructed to spit the tablet). The FENTORA tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed. The FENTORA tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 15-25 minutes. After 30 minutes, if remnants from the FENTORA 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 FENTORA in the buccal cavity.

FENTORA® (fentanyl buccal tablet), CII

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

<table>
<thead>
<tr>
<th>Current ACTIQ Dose (mcg)</th>
<th>Initial FENTORA Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100 mcg tablet</td>
</tr>
<tr>
<td>400</td>
<td>100 mcg tablet</td>
</tr>
<tr>
<td>600</td>
<td>200 mcg tablet</td>
</tr>
<tr>
<td>800</td>
<td>200 mcg tablet</td>
</tr>
<tr>
<td>1200</td>
<td>2 x 200 mcg tablets</td>
</tr>
<tr>
<td>1600</td>
<td>2 x 200 mcg tablets</td>
</tr>
</tbody>
</table>

### 2.7 Discontinuation of FENTORA

For patients no longer requiring opioid therapy, consider discontinuing FENTORA 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, FENTORA therapy can usually be discontinued immediately (see Drug Abuse and Dependence [9.3]).

**2.8 Disposal of FENTORA**

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush FENTORA blister packages or cartons down the toilet. If you need additional assistance with disposal of FENTORA, call Teva Pharmaceuticals at 1-888-463-8279.

### 3 DOSAGE FORMS AND STRENGTHS

FENTORA 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

FENTORA is contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients (see Indications and Usage [1]; Warnings and Precautions [5.1]).
- Significant respiratory depression (see Warnings and Precautions [5.1]).
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department (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 [5.9]).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (see Warnings and Precautions [5.4]).
- Known hypersensitivity (e.g., anaphylaxis) to fentanyl or components of FENTORA (e.g., anaphylaxis) (see Adverse Reactions [6.2]).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, support of respiration, and use of opioid antagonists, depending on the patient’s clinical status (see Overdose [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 use of FENTORA, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of FENTORA.

To reduce the risk of respiratory depression, proper dosing and titration of FENTORA are essential (see Dosage and Administration [2.4]). Overestimating the FENTORA dosage can result in a fatal overdose with the first dose. The substitution of FENTORA for any other fentanyl product may result in fatal overdose (see Warnings and Precautions [5.5]).

FENTORA 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 FENTORA, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

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

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. CSA 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 FENTORA. 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 the importance of calling 911 or getting emergency medical help, even if naloxone is administered (see Patient Counseling Information [17]).

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

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

FENTORA could be fatal to children for whom it is not prescribed and for whom it is not opioid-tolerant. Accidental ingestion of even one dose of FENTORA, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

Patients and their caregivers must be informed that FENTORA contains a medicine in an amount sufficient to cause serious, life-threatening, or fatal respiratory depression in children (including children or other close contacts at risk for accidental ingestion or overdose). If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone (see Warnings and Precautions [5.4, 5.6], Patient Counseling Information [17]).

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

FENTORA could be fatal to children for whom it is not prescribed and for whom it is not opioid-tolerant, accidental ingestion of even one dose of FENTORA, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

In children, accidental ingestion of even one dose of FENTORA could be fatal to children for whom it is not prescribed and for whom it is not opioid-tolerant.
FENTORA® (fentanyl buccal tablet), CII

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

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

Concomitant use of FENTORA 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 (5.3)], particularly when an inhibitor is added after a stable dose of FENTORA is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in FENTORA-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using FENTORA with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in FENTORA-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of FENTORA based on the drug effects associated with the concomitant use of the Drug Interactions (7).

Concomitant use of FENTORA with CYP3A4 inhibitors or discontinuation of a CYP3A4 inducer 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 FENTORA with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider dosage adjustment of FENTORA to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see Drug Interactions (7)].

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

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of death compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see Dosage and Administration (2.2), Warnings and Precautions (5.4)].

5.5 Risk of Median Epidural Error

When prescribing, do not convert a patient to FENTORA from any other fentanyl product on a mcg per mcg basis as FENTORA and other fentanyl products are not equivalent on a microgram per microgram basis. Therefore, for opioid tolerant patients, the initial dose of FENTORA 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 include the following:

• Prescribers for outpatient use must be certified with the REMS program by enrolling and completing training. Prescribers must document opioid tolerance with every prescription.

• Outpatients must be enrolled in the REMS program and must be opioid-tolerant to receive FENTORA [see Dosage and Administration (2.2)].

• Outpatient pharmacies must be certified with the REMS program and verify documentation of opioid tolerance with every prescription.

• Certified pharmacies must be notified by the REMS program and develop policies and procedures to verify opioid tolerance in inpatients who require FENTORA while hospitalized.

• Wholesale and distributors must enroll in the REMS program and distribute only to certified pharmacies.

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

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of FENTORA during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and may require resuscitative interventions [see Warnings and Precautions (5.8)].

FENTORA 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 include the following:

• Prescribers for outpatient use must be certified with the REMS program by enrolling and completing training. Prescribers must document opioid tolerance with every prescription.

• Outpatients must be enrolled in the REMS program and must be opioid-tolerant to receive FENTORA [see Dosage and Administration (2.2)].

• Outpatient pharmacies must be certified with the REMS program and verify documentation of opioid tolerance with every prescription.

• Certified pharmacies must be notified by the REMS program and develop policies and procedures to verify opioid tolerance in inpatients who require FENTORA while hospitalized.

• Wholesale 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.

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

FENTORA is available in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

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 Drug Abuse and Dependence (5.7)], FENTORA 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 include the following:

• Prescribers for outpatient use must be certified with the REMS program by enrolling and completing training. Prescribers must document opioid tolerance with every prescription.

• Outpatients must be enrolled in the REMS program and must be opioid-tolerant to receive FENTORA [see Dosage and Administration (2.2)].

• Outpatient pharmacies must be certified with the REMS program and verify documentation of opioid tolerance with every prescription.

• Certified pharmacies must be notified by the REMS program and develop policies and procedures to verify opioid tolerance in inpatients who require FENTORA while hospitalized.

• Wholesale 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.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of FENTORA 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., diarrhea, nausea). Therefore, or opioid tolerant patients, the initial dose of FENTORA 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)].

6.6 Drug Interactions

Any 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 added after a stable dose of FENTORA is achieved. Use in such patients necessitates intensive counseling about the risks and proper use of FENTORA along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see Dosage and Administration (2.2), Warnings and Precautions (5.4)].
Interactions (7). Monitor these patients for signs of hypotension after initiating or titrating the dosage of FENTORA. In patients with circulatory shock, FENTORA may cause vasodilatation that can further reduce cardiac output and blood pressure. Avoid the use of FENTORA in patients with circulatory shock.

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

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), FENTORA 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 FENTORA. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of FENTORA in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions

FENTORA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The fentanyl in FENTORA may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

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

5.16 Risks of Driving and Operating Machinery

FENTORA 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 FENTORA and know how they will react to the medication.

5.17 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use FENTORA with caution in patients with bradycardia/arrhythmias.

5.18 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:

- Life-Threatening Respiratory Depression
- Interactions with Benzodiazepines and Other CNS Depressants
- Addiction, Abuse, and Misuse
- Neonatal Opioid Withdrawal Syndrome
- Serotonin Syndrome
- Adrenal Insufficiency
- Severe Hypotension
- Gastrointestinal Adverse Reactions
- Seizures

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 FENTORA 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 FENTORA were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as oxycodone for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of FENTORA therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

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

Application Site Reactions: In clinical trials, 10% of all patients exposed to FENTORA reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥5% 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 FENTORA varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving FENTORA. Events are classified by system organ class.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>MedDRA preferred term, n (%)</th>
<th>100 mcg (N=34)</th>
<th>200 mcg (N=53)</th>
<th>400 mcg (N=53)</th>
<th>600 mcg (N=56)</th>
<th>800 mcg (N=113)</th>
<th>Total (N=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>4 (9)</td>
<td>5 (15)</td>
<td>10 (19)</td>
<td>13 (23)</td>
<td>18 (31)</td>
<td>50 (17)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>4 (7)</td>
<td>13 (23)</td>
<td>3 (3)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>3 (7)</td>
<td>1 (3)</td>
<td>9 (17)</td>
<td>1 (2)</td>
<td>5 (4)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>5 (11)</td>
<td>2 (6)</td>
<td>12 (23)</td>
<td>18 (32)</td>
<td>21 (19)</td>
<td>58 (19)</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>6 (12)</td>
<td>7 (13)</td>
<td>3 (3)</td>
<td>20 (7)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>1 (2)</td>
<td>3 (9)</td>
<td>4 (8)</td>
<td>8 (14)</td>
<td>10 (9)</td>
<td>26 (9)</td>
</tr>
</tbody>
</table>

*Three hundred and two (302) patients were included in the safety analysis.
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:
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.
- Adrenocortical insufficiency: Cases of adrenal insufficiency have been reported with opioid use, often following greater than one month of use.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids (see Clinical Pharmacology (12.2)).

Endocrine Disorders:

- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in FENTORA.

Immunologic System Disorders:
- Hypersensitivity: The use of FENTORA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome (see Warnings and Precautions (5.8)). Available data with FENTORA in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observed newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly (see Warnings and Precautions (5.8)), Labor or Delivery. Opioids across the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. FENTORA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including FENTORA, 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 dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

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

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

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

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with FENTORA.

Table 4. Clinically Significant Drug Interactions with FENTORA

Inhibitors of CYP3A4

Clinical Impact: The concomitant use of FENTORA 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 FENTORA is achieved (see Warnings and Precautions (5.3)). After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease (see Clinical Pharmacology (12.3)), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.

Intervention: If concomitant use is necessary, consider dosage reduction of FENTORA until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the FENTORA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Examples: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice

CYP3A4 Inducers

Clinical Impact: The concomitant use of FENTORA and CYP3A4 inducers can decrease the plasma concentration of fentanyl (see Clinical Pharmacology (12.3)), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl (see Warnings and Precautions (5.3)). After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase (see Clinical Pharmacology (12.3)), which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

Intervention: If concomitant use is necessary, consider increasing the FENTORA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider FENTORA dosage reduction and monitor for signs of respiratory depression.

Examples: Rifampin, carbamazepine, phenytoin

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Clinical Impact: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Intervention: Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribingnaloxone for the emergency treatment of opioid overdose (see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.4)).

Examples: Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Serotonergic Drugs

Clinical Impact: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome (see Warnings and Precautions (5.8)).

Intervention: If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue FENTORA if serotonin syndrome is suspected.

 Examples: Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), triyclic antidepressants (TCAs), vaptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous metylene blue).

Monoamine Oxidase Inhibitors (MAOIs)

Clinical Impact: MAOIs interactions with opioids may manifest as serotonin syndrome (see Warnings and Precautions (5.3)) or opioid toxicity (e.g., respiratory depression, coma) (see Warnings and Precautions (5.3)).

Intervention: The use of FENTORA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

Examples: Phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Clinical Impact: May reduce the analgesic effect of FENTORA and/or precipitate withdrawal symptoms.

Intervention: Avoid concomitant use.

Examples: Butorphanol, nalbuphine, pentazocine, buprenorphine

Muscle Relaxants

Clinical Impact: Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Intervention: Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of FENTORA and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose (see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.4)).

Examples: cyclobenzaprine, metaxalone

Diuretics

Clinical Impact: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs

Clinical Impact: The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Intervention: Monitor patients for signs of urinary retention or reduced gastric motility when FENTORA is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome (see Warnings and Precautions (5.8)). Available data with FENTORA in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes in the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observed newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly (see Warnings and Precautions (5.8)), Labor or Delivery. Opioids across the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. FENTORA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including FENTORA, 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 dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.
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 7-8 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. A reduction in fetal weights was seen in the study (250 mcg/kg dose is equivalent to 7-8 times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

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

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 FENTORA per pain episode on a mg/m² basis and produced mean steady-state plasma levels that are approximately 5 times higher than the mean Cmax observed following administration of 800 mcg dose of FENTORA 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 Lab Test
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 FENTORA.

Clinical Considerations
Monitor infants exposed to FENTORA 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
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2) Clinical Pharmacology (12.2), Nonclinical Toxicology (31)].

8.4 Pediatric Use
The safety and efficacy of FENTORA 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 FENTORA, 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 FENTORA 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 single 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 FENTORA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.3)].

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

8.6 Patients with Renal or Hepatic Impairment
Insufficient information exists to make recommendations regarding the use of FENTORA 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
Population pharmacokinetic analyses of fentanyl revealed that the pharmacokinetic effects of race with the use of FENTORA 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
FENTORA contains fentanyl, a Schedule II controlled substance. Abuse
FENTORA contains fentanyl, a substance with high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadone. FENTORA can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.6)].

Abuse of opioids with rapid onset of action requires careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling use of its, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking behavior can 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 health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated disease. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance [see Drug Abuse and Dependence (9.3)]. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction to FENTORA, like other opioids, can be diverted for non-medical use into illicit circles of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Physical dependence may also occur in patients, proper prescribing practices, periodic re-evaluation of therapy, and appropriate dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

9.2 Abuse
FENTORA is for oral transmucosal use only. Abuse of FENTORA poses a risk of overdose and death. This risk is increase use and includes: a strong desire to take the drug, difficulties in controlling use of its, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal.

9.3 Dependence
Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) mixed agonist/antagonist activity (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.5)].

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

Additionally, cardiovascular effects observed with opioid overdose include hypotension and respiratory depression [see Warnings and Precautions (5.3)].

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

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in FENTORA, closely 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 an 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...
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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, pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension. 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 (5.1)].

12.3 Pharmacokinetics

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

Absorption

Following buccal administration of FENTORA, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of FENTORA 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 FENTORA and ACTIQ (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with FENTORA) (Table 5).

Table 5. Pharmacokinetic Parameters in Adult Subjects Receiving FENTORA or ACTIQ

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter (mean)</th>
<th>FENTORA 400 mcg</th>
<th>ACTIQ 400 mcg (adjusted dose)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Bioavailability</td>
<td>65% ± 20%</td>
<td>47% ± 10.5%</td>
</tr>
<tr>
<td>Fraction Absorbed Transmucosally</td>
<td>48% ± 31.8%</td>
<td>22% ± 13.7%</td>
</tr>
<tr>
<td>Tmax (minute)**</td>
<td>46.8 (20-240)</td>
<td>90.8 (35-240)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1.02 ± 0.42</td>
<td>0.63 ± 0.21</td>
</tr>
<tr>
<td>AUCinf (ng•hr/mL)</td>
<td>0.40 ± 0.13</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td>AUCcorr (ng•hr/mL)</td>
<td>6.48 ± 2.98</td>
<td>4.79 ± 1.96</td>
</tr>
</tbody>
</table>

*Based on venous blood samples.
**Data for Tmax presented as median (range).
***ACTIQ data was dose adjusted (800 mcg to 400 mcg).

Similarly, in another bioavailability study exposure following administration of FENTORA was also greater (approximately 50%) compared to Actiq. Due to differences in drug delivery, measures of exposure (Cmax, AUCcorr, AUCinf) associated with a given dose of fentanyl were substantially greater with FENTORA 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) and Warnings and Precautions (5.1)]. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median Tmax for FENTORA.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of FENTORA 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.
FENTORA® (fentanyl buccal tablet), CII

0

800 mcg Doses of FENTORA in Healthy Subjects

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

Table 7. Pharmacokinetic Parameters in Patients with Mucositis

<table>
<thead>
<tr>
<th>FENTORA Dose (ng/mL)</th>
<th>Mean (SE) Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mcg</td>
<td>3.0 (0.12)</td>
</tr>
<tr>
<td>200 mcg</td>
<td>4.4 (0.14)</td>
</tr>
<tr>
<td>400 mcg</td>
<td>5.3 (0.21)</td>
</tr>
<tr>
<td>600 mcg</td>
<td>5.8 (0.13)</td>
</tr>
<tr>
<td>800 mcg</td>
<td>6.4 (0.15)</td>
</tr>
</tbody>
</table>

6 HOW SUPPLIED/STORAGE AND HANDLING

FENTORA is 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 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.

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Debossing</th>
<th>Carton/Blister Package Color</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mcg</td>
<td>1</td>
<td>Blue</td>
<td>NDC 63459-541-28</td>
</tr>
<tr>
<td>200 mcg</td>
<td>2</td>
<td>Orange</td>
<td>NDC 63459-542-28</td>
</tr>
<tr>
<td>400 mcg</td>
<td>4</td>
<td>Sage green</td>
<td>NDC 63459-544-28</td>
</tr>
<tr>
<td>600 mcg</td>
<td>6</td>
<td>Magenta (pink)</td>
<td>NDC 63459-546-28</td>
</tr>
<tr>
<td>800 mcg</td>
<td>8</td>
<td>Yellow</td>
<td>NDC 63459-548-28</td>
</tr>
</tbody>
</table>

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.
FENTORA® (fentanyl buccal tablet), CII

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

FENTORA 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 FENTORA
FENTORA 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 pharmacists must develop policies and procedures to verify opioid tolerance in inpatients who require FENTORA while hospitalized [see Warnings and Precautions (5.7)].

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from coadministration 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 FENTORA while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking FENTORA [see Warnings and Precautions (5.10); Drug Interactions (7)].

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening emergency. Patients with abnormal baseline adrenal function, those who have not maintained an adequate level of adrenal reserve, or those with other factors that may increase the risk of adrenal insufficiency (e.g., hypothyroidism, hypopituitarism) may be at increased risk. Patients taking opioids with unspecified monoamine oxidase inhibitors may be at increased risk of adrenal insufficiency. Instruct patients to report symptoms of adrenal insufficiency to their healthcare provider.

Important Administration Instructions [see Dosage and Administration (2)]
• Instruct patients not to take FENTORA 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 FENTORA 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 FENTORA.
• Instruct patients that the titration phase is the period in which they may take more than ONE tablet to achieve 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 FENTORA USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of FENTORA for any breakthrough pain episode.
• Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with FENTORA.
• Instruct patients NOT to share FENTORA and that sharing FENTORA with anyone else could result in the other individual’s death due to overdose.
• Make patients aware that FENTORA contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
• Instruct patients to not open the blister until ready to use FENTORA 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 FENTORA tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are 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 doctor if breakthrough pain is not alleviated or worsens after taking FENTORA.
• Instruct patients to use FENTORA exactly as prescribed by their doctor and not to take FENTORA more often than prescribed.
• Provide patients and their caregivers with a Medication Guide each time FENTORA is dispensed because new information may be available.

Hypotension
Inform patients that FENTORA 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 (5.2), Anaphylaxis].

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

Pregnancy
Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of FENTORA 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 FENTORA can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)].
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see Use in Specific Populations (8.2)].

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

Driving or Operating Heavy Machinery
Inform patients that FENTORA may impair the ability to perform potentially hazardous activities such as driving 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 (5.3)].

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see Adverse Reactions (6), Clinical Pharmacology (2.2)].

Dispense with Medication Guide available at: www.tevausa.com/medguides

FENTORA® (fentanyl buccal tablet), CII

Medication Guide
FENTORA® (fen-tor-a) (fentanyl) buccal tablet, CII

IMPORTANT:
Do not use FENTORA 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 you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep FENTORA in a safe place away from children.

Get emergency help right away if:
- a child takes FENTORA. FENTORA can cause an overdose and death in any child who takes it.
- an adult who has not been prescribed FENTORA uses it.
- an adult who is not already taking opioids around-the-clock, uses FENTORA.

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

FENTORA 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. FENTORA 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 FENTORA 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 FENTORA:
- Get emergency help or call 911 right away if you take too much FENTORA (overdose). When you first start taking FENTORA, when your dose is changed, or if you take too much (overdose), serious 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 FENTORA 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 FENTORA. They could die from taking it. Selling or giving away FENTORA is against the law.
- Store FENTORA 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 FENTORA. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.

FENTORA is available only through a program called the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS). To receive FENTORA, you must:
- talk to your healthcare provider
- understand the benefits and risks of FENTORA
- agree to all of the instructions
- sign the Patient Enrollment Form

FENTORA is only available at pharmacies that are part of the TIRF REMS. Your healthcare provider can help you locate a pharmacy closest to your home where you can have your FENTORA prescription filled.

Do be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

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

Do not take FENTORA 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 FENTORA. See the end of this Medication Guide for a complete list of ingredients in FENTORA.
- 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 FENTORA, 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
- Abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems
- 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

Tell your healthcare provider if you are:
- Pregnant or planning to become pregnant. Prolonged use of FENTORA during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- Breastfeeding. FENTORA passes into breast milk and may harm your baby.
- Living in a household where there are small children or someone who has abused street or prescription drugs.
- Taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking FENTORA with certain other medicines can cause serious side effects that could lead to death.

When taking FENTORA:
- Do not change your dose. Take FENTORA exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your body have become used to the medicine (you are opioid tolerant). Do not use FENTORA if you are not opioid tolerant.
- See the detailed Instructions for Use at the end of this Medication Guide for information about how to use FENTORA.
- Use FENTORA tablets whole.
- Do not crush, split, suck, or chew FENTORA tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.

continued
**FENTORA® (fentanyl buccal tablet), CII**

- Wait 30 minutes after using FENTORA. If there is any of the FENTORA 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 FENTORA for each episode of breakthrough cancer pain.
- Use 1 dose of FENTORA for an episode of breakthrough cancer pain.
- If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of FENTORA, you can use only 1 more dose of FENTORA as instructed by your healthcare provider.
- If your breakthrough pain does not get better after the second dose of FENTORA, call your healthcare provider for instructions. **Do not use another dose of FENTORA at this time.**
- Wait at least 4 hours before treating a new episode of breakthrough cancer pain with FENTORA.
- If you only need to take 1 dose of FENTORA for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of FENTORA for a new episode of breakthrough pain.
- If you need to use 2 doses of FENTORA for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of FENTORA for a new episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using FENTORA.
- Talk to your healthcare provider if your dose of FENTORA does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of FENTORA 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 FENTORA 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 FENTORA is no longer needed, see “**How should I dispose of unused FENTORA tablets when they are no longer needed?”** for proper disposal of FENTORA.
- Dispose of expired, unwanted, or unused FENTORA 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 FENTORA affects you. FENTORA 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 FENTORA may cause you to overdose and die.
- **DO NOT** Switch from FENTORA to other medicines that contain fentanyl without talking with your healthcare provider. The amount of fentanyl in a dose of FENTORA is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of FENTORA that may be different than other fentanyl containing medicines you may have been taking.

### The possible side effects of FENTORA:

- 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.

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**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 FENTORA 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 FENTORA until you have talked to your healthcare provider.

These are not all the possible side effects of FENTORA. 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

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**How should I store FENTORA?**

- Always keep FENTORA in a safe place away from children and from anyone for whom it has not been prescribed. Protect FENTORA from theft.
- Store FENTORA at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze FENTORA.
- Keep FENTORA in the original blister unit. Do not remove FENTORA from its blister packaging for storage in a temporary container, such as a pill box.
- Keep FENTORA dry.

**How should I dispose of unused FENTORA tablets when they are no longer needed?**

- Dispose of any unused FENTORA 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 FENTORA packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of FENTORA, call Teva Pharmaceuticals at 1-888-483-8279 or call your local Drug Enforcement Agency (DEA) office.

**General Information about FENTORA**

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

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

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-886-822-1483.

**What are the ingredients in FENTORA?**

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

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

- **FENTORA comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA 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 FENTORA tablets will be printed in the boxed area shown as

(See Figure 1).

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

- Do not push the tablet through the foil on the blister because this could damage the tablet.
- When removed from the blister unit, FENTORA tablet must be used right away.
- Use FENTORA tablets whole.
- Do not crush, split, suck, or chew FENTORA tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.
- You can place a FENTORA 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.

(See Figure 3).

- 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).

- OR,
  - on the floor of your mouth, under your tongue (See Figures 4a, 4b, 4c, 4d).

- After 30 minutes, if there is any FENTORA left in your mouth, you may drink a glass of water to help you swallow the leftover medicine.
- If you cannot use FENTORA in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do.