FENTORA® (fentanyl buccal tablet), CII
Initial U.S. Approval: 1968

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

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

See full prescribing information for complete boxed warning.

- Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, FENTORA is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraine (1). (2.1, 2.2)
- 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, 12.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)
- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to FENTORA. (5.5)
- When dispensing, do not substitute with any other fentanyl products. (5.5)
- FENTORA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient’s risk before prescribing and monitor closely for these behaviors and conditions. (5.6)
- FENTORA is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe for patients, pharmacies, and distributors are required to enroll in the program. (5.7)
- Prolonged use of FENTORA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)

RECENT MAJOR CHANGES
Boxed Warning: 12/2016
Dosage and Administration (2): 12/2016
Contraindications (4): 12/2016
Warnings and Precautions (5): 12/2016

INDICATIONS AND USAGE
FENTORA is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

RECENT MAJOR CHANGES

Full Prescribing Information: Contents

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

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2 DOSAGE AND ADMINISTRATION
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5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

DOSE FORMS AND STRENGTHS
Buccal Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (5)

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

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or In Elderly, Cachectic, or Debilitated Patients; Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue 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. (5.11)
- 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, asthma, dehydration and headache. (6.1)

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

DRUG INTERACTIONS
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with 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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FENTORA® (fentanyl buccal tablet), CII

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FULL PRESCRIBING INFORMATION

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

Life-Threatening Respiratory Depression
Serious life-threatening and/or fatal respiratory depression has occurred in patients treated with FENTORA, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of FENTORA or following a dose increase. The substitution of FENTORA for any other fentanyl product may result in fatal overdose (see Warnings and Precautions (5.1)). Due to the risk of respiratory depression, FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients (see Contraindications (4)).

Accidental Ingestion
Accidental ingestion of even one dose of 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)).

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

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

Reserve concomitant prescribing of FENTORA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

Risk of Medication Errors
Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose (see Dosage and Administration (2.1), Warnings and Precautions (5.5)).

When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to FENTORA (see Dosage and Administration (2.1)).

When dispensing, do not substitute a FENTORA prescription for other fentanyl products.
Initiate the dosing regimen for each patient individually, taking into account the patient’s history 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 (5.1)].

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 (5.2, 5.6)]. Patient Counseling Information (17).

FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg for 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 (5.2)].

2.2 Initial Dosage

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

Patients on ACTIQ

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

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

<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>

*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.

2.3 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 use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg FENTORA tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.

c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of 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 take a maximum of two doses of FENTORA tablets available at any time.

e. Patients should be strongly encouraged to use all of their FENTORA tablets of one strength per breakthrough pain episode.

2.4 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).

2.5 Administration of FENTORA

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer FENTORA.

2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.

3. Bend the blister unit along the line where indicated.

4. Peel back the blister backing to expose the tablet. Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.

5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

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

2.6 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing FENTORA along with a gradual downward 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)]

2.7 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 1-888-489-8279.

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:

• Known or suspected gastrointestinal obstruction, including paralytic ileus

• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment

• Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department

• Known or suspected gastrointestinal obstruction, including paralytic ileus

• 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, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of 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 (2.3)]. 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 (5.2)].

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.

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

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

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

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

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

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

Concomitant use of 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 Drug Interactions (7.9)] (pain patients)] (17)]. Counselling the patient that 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 until stable drug effects are achieved [see Drug Interactions (7)].

Concomitant use of FENTORA with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, increase the likelihood of 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 increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal develop [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 FENTORA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine hypnotics, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related deaths compared to opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressants 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, monitor patients closely at frequent intervals and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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

5.5 Risk of Medication Errors

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

There are no safe conversion directions available for patients on any other fentanyl products except ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of FENTORA should always be 100 mcg. Individualize titrate each patient’s dose to provide adequate analgesia while minimizing side effects [see Dosage and Administration (2.3)].

5.6 Addiction, Abuse, and Misuse

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

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed FENTORA. Addiction can occur at recommended doses and the drug is misused or abused. Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing FENTORA, and monitor all patients receiving FENTORA for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance use disorder, patients who used high-risk substances (including alcohol and other drugs) while receiving opioids, and younger patients.

Monitor such patients closely, particularly when initiating and titrating FENTORA and for any other concurrent treatment options are inadequate.

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

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

Required components of the TIRF REMS Access program are:

• Healthcare professionals, who prescribe FENTORA for outpatient use, must enroll in the program, and distribute only to authorized pharmacies.

• Healthcare professionals, who prescribe FENTORA for inpatient use, must enroll in the program, and comply with the REMS requirements.

• Healthcare professionals, who prescribe FENTORA for inpatient use, must enroll in the program, and distribute only to authorized pharmacies.

• Wholesale and distributors that distribute FENTORA must enroll in the program, and distribute only to authorized pharmacies.

• Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFRFREMSAccess.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 if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), Patient Counseling Information (17)].

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Emphysema

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

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

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

Monitor such patients closely, particularly when initiating and titrating FENTORA and when FENTORA is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.1)].

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
noradrenergic reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), trizipans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and others, such as linezolid and intravenous mexiteline ) [see Drug Interactions (7)]. The following adverse reactions are included 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 abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue FENTORA if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including anemia, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see Drug Interactions (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of FENTORA. In patients with circulatory shock, FENTORA may cause vasodilation 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 inspiratory 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

The fentanyl in 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 bradyarrhythmias.

5.18 Application Site Reactions

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

5.19 MAO Inhibitors

FENTORA is not recommended for use in patients who have received MAO inhibitors within 14 days, because of unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics [see Drug Interactions (7)].

6 ADVERSE REACTIONS

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

• Life-Threatening Respiratory Depression [see Warnings and Precautions (5.1)]

• Interactions with Benzodiazepines and Other CNS Depressants [see Warnings and Precautions (5.4)]

• Addiction, Abuse, and Misuse [see Warnings and Precautions (5.6)]

• Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.8)]

• Serotonin Syndrome [see Warnings and Precautions (5.10)]

• Adrenal Insufficiency [see Warnings and Precautions (5.11)]

• Severe Hypotension [see Warnings and Precautions (5.12)]
FENTORA® (fentanyl buccal tablet), CII

**Table 4: Clinically Significant Drug Interactions with FENTORA**

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7 DRUG INTERACTIONS

**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.

**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)].

**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.

**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 [see Warnings and Precautions (5.4)].

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

**Clinical Impact:** The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see Warnings and Precautions (5.10)].

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

**Examples:** Selective serotonin reuptake inhibitors (SSRIs), serotonin and nor-epinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

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

FENTORA® (fentanyl buccal tablet), CII

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**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)].

**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 [see Warnings and Precautions (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 (5.10)].

**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 nor-epinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)

Clinical Impact: MAOI interactions with opioids may manifest as serotonin syndrome [see Warnings and Precautions (5.10)] or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.11)].

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/Agonist 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.

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 dosage. 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 dosage. No evidence of malformations or other adverse outcomes was 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 may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Fentanyl (25, 50, or 100 mcg/kg) was administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen. The study (100 mg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rats during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses ≥100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl has been shown to 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 15 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 reported.

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.

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome among human 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 breast-feeding is stopped.

8.2 Lactation

Risk Summary

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

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

Clinical Considerations

Fentanyl or opioid analgesics administered to pregnant women during labor may vary. Observe newborns for symptoms of neonatal respiratory or neurological depression. Data

Human Data

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

Animal Data

Fentanyl (25, 50, or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen. The study (100 mg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses ≥100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl has been shown to 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 15 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 reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day being 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.

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

Safety and 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 below the age of 18 years. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Fentanyl (50, 100, or 250 mcg/kg) was 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 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.
FENTORA® (fentanyl buccal tablet), CII

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 isozyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

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

8.8 Race
The pharmacokinetic effects of the 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.

9.2 Abuse
FENTORA contains fentanyl, a substance with high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. FENTORA can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.6)]. All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once the intent to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal. "Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance [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.

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

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

Risks Specific to the Abuse of FENTORA
FENTORA is for oral transmucosal use only. Abuse of FENTORA poses a risk of overdose and death. This risk is increased with concurrent abuse of FENTORA with alcohol and other central nervous system depressants.

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

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

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

10 OVERDOSAGE

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

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

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose. Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in FENTORA, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information.

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

11 DESCRIPTION
FENTORA (fentanyl buccal tablet) is an opioid agonist, intended for buccal mucosal administration. FENTORA is designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

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

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

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

**Effects on the Cardiovascular System**
Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension.

**Effects on the Endocrine System**
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [see Adverse Reactions (6.2)]. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

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

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

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals [see Dosage and Administration (2.1)]. The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [see Dosage and Administration (2.1, 2.4)].

**Concentration-Adverse Reaction Relationships**
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2, 2.3, 2.4)].

**Respiratory System**
All opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of 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 (6.1)].

### 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% ± 17.3%</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (minute)**</td>
<td>46.8 (20-240)</td>
<td>90.8 (35-240)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1.02 ± 0.42</td>
<td>0.63 ± 0.21</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tmax&lt;/sub&gt; (ng•hr/mL)</td>
<td>0.40 ± 0.18</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (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 T<sub>max</sub> 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 (C<sub>max</sub>, AUC<sub>0-tmax</sub>, AUC<sub>0-inf</sub>) 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 (2.2) and Warnings and Precautions (5.3)]. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T<sub>max</sub> 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.

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

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter (mean±SD)</th>
<th>100 mcg</th>
<th>200 mcg</th>
<th>400 mcg</th>
<th>800 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>0.25 ± 0.14</td>
<td>0.40 ± 0.18</td>
<td>0.97 ± 0.53</td>
<td>1.59 ± 0.90</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; minute** (range)</td>
<td>(25.0 - 1810.0)</td>
<td>(20.0 - 1800.0)</td>
<td>(20.0 - 1800.0)</td>
<td>(20.0 - 1800.0)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tmax&lt;/sub&gt; (ng•hr/mL)</td>
<td>0.09 ± 0.37</td>
<td>2.11 ± 1.13</td>
<td>4.72 ± 1.95</td>
<td>9.05 ± 3.72</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng•hr/mL)</td>
<td>1.47 ± 1.35</td>
<td>4.83 ± 2.13</td>
<td>10.19 ± 3.95</td>
<td>22.63 ± 8.32</td>
</tr>
</tbody>
</table>

* Based on venous sampling.

**Data for T<sub>max</sub> presented as median (range).

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

Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl. The effect of mucositis (Grade 1) on the pharmacokinetic profile of FENTORA was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected T<sub>max</sub> where range was used) are presented in Table 7.

**Table 7. Pharmacokinetic Parameters** Following FENTORA 400 mcg in Mucositis-Associated Mucositis

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>FENTORA 400 mcg (mucositis)</th>
<th>FENTORA 400 mcg (no mucositis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>0.92 ± 0.42</td>
<td>0.57 ± 0.21</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (minute)</td>
<td>58.5 (24-220)</td>
<td>41.8 (20-240)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-tmax&lt;/sub&gt; (ng•hr/mL)</td>
<td>2.04 ± 1.13</td>
<td>1.59 ± 0.87</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng•hr/mL)</td>
<td>7.26 ± 3.13</td>
<td>5.48 ± 2.32</td>
</tr>
</tbody>
</table>
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2.3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2.3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison).

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

Impairment of Fertility
In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 6 times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 14 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

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

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

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

Patients assessed pain intensity on a scale that rated the pain as 0-none to 10-worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45, and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline (SPID15) was the primary efficacy measure.

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

Table 8. Successful Dose of FENTORA Following Initial Titration

<table>
<thead>
<tr>
<th>FENTORA Dose</th>
<th>n (%)</th>
<th>(N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mcg</td>
<td>13 (16)</td>
<td></td>
</tr>
<tr>
<td>200 mcg</td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>400 mcg</td>
<td>21 (26)</td>
<td></td>
</tr>
<tr>
<td>600 mcg</td>
<td>10 (13)</td>
<td></td>
</tr>
<tr>
<td>800 mcg</td>
<td>25 (31)</td>
<td></td>
</tr>
</tbody>
</table>

The LS mean (SE) SPID15 for FENTORA-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING
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 is debossed on one side with BFT, and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

<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 63459-54-28</td>
</tr>
<tr>
<td>200 mcg</td>
<td>2</td>
<td>Orange</td>
<td>NDC 63459-54-28</td>
</tr>
<tr>
<td>400 mcg</td>
<td>4</td>
<td>Sage green</td>
<td>NDC 63459-54-28</td>
</tr>
<tr>
<td>600 mcg</td>
<td>6</td>
<td>Magenta (pink)</td>
<td>NDC 63459-54-28</td>
</tr>
<tr>
<td>800 mcg</td>
<td>8</td>
<td>Yellow</td>
<td>NDC 63459-54-28</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.

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.) Protect FENTORA from freezing and moisture. Do not use if the blister package has been tampered with.

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting FENTORA or when the dosage is increased, and that it can occur even at recommended dosages [see Warnings and Precautions (5.1)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Ingestion
• Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure [see Warnings and Precautions (5.2)].
• Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see Warnings and Precautions (5.2)].
• Instruct patients to take steps to store FENTORA securely and to dispose of unused FENTORA. [see Dosage and Administration (2.7), Patient Counseling Information; Disposal of Unopened FENTORA Blister Packages When No Longer Needed (17)].
• Instruct patients and caregivers to keep both used and unused FENTORA out of the reach of children [see Warnings and Precautions (5.2)].

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)

Instruct patients that potentially fatal additive effects from FENTORA if used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see Warnings and Precautions (5.4), Drug Interactions (7)].

Addiction, Abuse, and Misuse

Inform patients about the appropriate use of FENTORA, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see Warnings and Precautions (5.6)]. Instruct patients not to share FENTORA with others and to take steps to protect FENTORA from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Advise patients of the following information pertaining to the TIRF REMS

• Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive FENTORA.
• Allow patients the opportunity to ask questions and discuss any concerns regarding FENTORA or the TIRF REMS Access program.
• As required by the TIRF REMS Access program, review the contents of the FENTORA Medication Guide with every patient before initiating treatment with FENTORA.
• Advise the patient that FENTORA is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number for the website for information on how to obtain the drug.
• Advise the patient that only enrolled healthcare providers may prescribe FENTORA.
• Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of FENTORA.
• Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program [see Warnings and Precautions (5.7)].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their 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, 5.19), Drug Interactions (7)].

Adrenal Insufficiency

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

Important Administration and Use Information

• Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
• Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take ONLY ONE ADDITIONAL DOSE OF 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 taking 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 not to 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.

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 (5.12)].

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)].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, and feeding difficulties. 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 a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see Warnings and Precautions (5.16)].

Conception

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

Disposal of Unopened FENTORA Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush the FENTORA blister packages or cartons down the toilet.

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

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-888-483-8278) or seek assistance from their local DEA office.

FENTORA® (fentanyl buccal tablet), CII

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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 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.
- 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. Store FENTORA away from children and in a safe place to prevent stealing or abuse. Selling or giving away FENTORA is against the law.
- 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) Access program. 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-Prescriber Agreement form
- FENTORA is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your FENTORA prescription filled.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, 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, 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.
- 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).
- 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.
- 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 after 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.**

**continued**
• 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.
• 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.

Get emergency medical help 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.

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

• Do not push the tablet through the foil on the blister unit because this could damage the tablet.
• When removed from the blister unit, 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.

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

• Leave the tablet in place until it dissolves. A FENTORA tablet generally takes between 14 to 25 minutes to dissolve.

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