PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{N}FENTORA™

Fentanyl Buccal/Sublingual Effervescent Tablets

Buccal/Sublingual Effervescent Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg of fentanyl (as fentanyl citrate); Buccal or Sublingual

Opioid Analgesic

Distributed by:
Teva Canada Limited
Toronto, Ontario M1B 2K9

Manufactured for:
Teva Canada Innovation
Montréal, Quebec H2Z 1S8

Date of Initial Authorization:
November 21, 2013

Date of Revision:
June 27, 2023

Submission Control Number: 271126

RECENT MAJOR LABEL CHANGES

7 Warning and Precautions, General, Neurologic	06/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FENTORA (fentanyl buccal/sublingual effervescent tablets) is indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.

Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine daily or an equianalgesic dose of another opioid daily for a week or longer (see 7 WARNINGS AND PRECAUTIONS).

All patients starting treatment with FENTORA must begin with titration from the 100 mcg dose (see 4 DOSAGE AND ADMINISTRATION).

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, FENTORA is contraindicated in the management of acute or post-operative pain, including headache/migraine, dental pain or use in the emergency room.

Note: FENTORA is contraindicated in all post-operative pain, including post-operative cancer pain if the patient is not already opioid tolerant. The addition of the qualifier “non cancer” may be confusing as it could be interpreted to mean that FENTORA can be used for post-operative pain after surgery for cancer or post-operatively for cancer pain, both of which can occur in opioid non-tolerant patients. The term “post-operative” already implies that the pain is due to surgery and not to cancer.

FENTORA is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of opioids to treat cancer pain.

1.1 Pediatrics

(< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of FENTORA in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Evidence from clinical studies and experience suggests that use in the geriatric population is

associated with differences in safety or effectiveness (see 7.1.4 Geriatrics).
Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating FENTORA in elderly patients to provide adequate efficacy while minimizing risk.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

- Opioid non-tolerant patients (use in acute or post-operative pain, including headache/migraine, dental pain or use in the emergency room).

- Patients who are hypersensitive to the active substance, fentanyl citrate, or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. Anaphylaxis and hypersensitivity have been reported in association with the use of oral transmucosal fentanyl products.

- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).

- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).

- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.

- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.

- Patients with acute alcoholism, delirium tremens, and convulsive disorders.

- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.

- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Proper Patient Selection

- **FENTORA (fentanyl buccal/sublingual effervescent tablets) is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of opioids to treat cancer pain.**

- **FENTORA is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain.** Patients considered opioid-tolerant are those who have taken at least 60 mg of oral morphine daily, at least 25 mcg/hr of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

- **FENTORA is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis (see 2 CONTRAINDICATIONS).**

- **Fentanyl products which are designed to manage breakthrough pain, including FENTORA, should not be used in patients who are receiving partial opioid agonists such as buprenorphine or agents with some opioid effects such as tramadol (see 9.4 DRUG INTERACTIONS, Drug-Drug Interactions).**

Addiction, Abuse, and Misuse

- **FENTORA poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing FENTORA, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7 WARNINGS AND PRECAUTIONS). FENTORA should be stored securely to avoid theft or misuse.**

Life-threatening Respiratory Depression: OVERDOSE

- **Fatal respiratory depression has occurred in patients treated with FENTORA, including following use in opioid non-tolerant patients and improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.**

- **Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of FENTORA or following a dose increase.**

- **Due to the risk of respiratory depression, in opioid non-tolerant patients, FENTORA is contraindicated in the management of acute or post-operative pain, including headache/migraine, dental pain, or use in the emergency room.**

  Special care must be used when dosing with FENTORA.

- **If the breakthrough pain episode is not relieved, patients should wait at least 4 hours before taking another dose (see 4 DOSAGE AND ADMINISTRATION).**

- **The concomitant use of FENTORA with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression (see 9.4 DRUG INTERACTIONS, Drug-Drug Interactions).**

Accidental Exposure

- **Accidental ingestion of even one dose of FENTORA, especially by children, can result in a fatal overdose of fentanyl (see 4 DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).**

Neonatal Opioid Withdrawal Syndrome

- **Prolonged maternal use of FENTORA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7 WARNINGS AND PRECAUTIONS).**

Interaction with Alcohol

- **The co-ingestion of alcohol with FENTORA should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).**

Medication Errors

- **When prescribing, do not convert patients on a mcg per mcg basis from any other transmucosal fentanyl product to FENTORA. If patients are using other opioid-containing products for breakthrough pain, they MUST be started on FENTORA at the initial dose of 100 mcg.**

- **Regardless of the opioid dose used for the baseline cancer pain, patients beginning treatment with FENTORA must begin with titration from the 100 mcg dose (see 4 DOSAGE AND ADMINISTRATION).**

- **When dispensing, do not substitute a FENTORA prescription for any other fentanyl product. 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. As a result of these differences, the substitution of FENTORA for any other fentanyl product may result in fatal overdose. FENTORA is NOT a generic version of any other fentanyl product.**

- **Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All units must be kept out of the reach and sight of children and opened units properly discarded.**

- **Instruct patients of the hazards related to taking opioids including fatal overdose.**

Risks From Concomitant Use With Benzodiazepines, 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 7 WARNINGS AND PRECAUTIONS, Neurologic and 9 DRUG INTERACTIONS).**
  - **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.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- FENTORA (fentanyl buccal/sublingual effervescent tablets) is indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to continuous opioid therapy for their persistent baseline cancer pain. Patients considered opioid tolerant are those who are taking continuous medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg/hr of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

- Individually titrate FENTORA to a dose that provides adequate analgesia with tolerable side effects (see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

- The maximum single dose should not exceed 800 mcg. FENTORA should only be used ONCE per breakthrough cancer pain episode, i.e. FENTORA should not be re-dosed within an episode.

- During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after FENTORA, the patient may use a rescue medication (other than FENTORA, after 30 minutes) as directed by their healthcare provider.

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

- Use of FENTORA should be limited to four episodes of breakthrough pain per day. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the continuous opioid used for persistent pain should be re-evaluated.

4.2 Recommended Dose and Dosage Adjustment

- **Pediatrics:** Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics)

- **Adults**: FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose. The maximum single dose should not exceed 800 mcg.

  Dosing recommendations:

  - Starting Dose:
    All patients **MUST** begin treatment using 100 mcg FENTORA.

  - Dose Titration:
    Dose titration is the key to success with opioid analgesic therapy. Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.

    The dose of FENTORA is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by dose titration.

    Dosage adjustments should be based on the patient's clinical response.

  - Adjustment or Reduction of Dosage:
    Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including FENTORA. Withdrawal

(abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal from the drug, these symptoms are usually mild (see 7 WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

From the initial dose, patients should be closely followed by the prescriber and the dosage strength changed 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 physician to determine if a dosage adjustment is warranted.

Patients 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). Do not use more than 4 tablets simultaneously. **Doses above 800 mcg FENTORA should not be used**.

Once adequate pain relief is achieved with a dose between 100 and 800 mcg FENTORA, the patient should get a prescription for FENTORA of the dose determined by titration (i.e., 100, 200, 400, 600 or 800 mcg) to treat subsequent episodes.

To reduce the risk of overdose during titration, patients should have only one strength of FENTORA tablets available at any time.

During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after FENTORA, the patient may use a rescue medication (other than FENTORA, after 30 minutes) as directed by their healthcare provider.

- Maintenance Dosing:
  Once titrated to an effective dose, patients should use **only ONE** FENTORA tablet of the appropriate strength per breakthrough pain episode.

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

  During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after FENTORA, the patient may use a rescue medication (other than FENTORA, after 30 minutes) as directed by their healthcare provider.

  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.

  If the patient experiences greater than four breakthrough pain episodes per day, the dose of the continuous opioid used for persistent pain should be re-evaluated.

- Discontinuation of Therapy:
  For patients requiring discontinuation of all opioid therapy, the recent FENTORA dose should be taken into consideration for a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects (see 7 WARNINGS AND PRECAUTIONS).

  If patients continue to take their background opioid therapy for persistent pain, FENTORA therapy may usually be immediately discontinued if no longer required for breakthrough pain.

  Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including FENTORA. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

  Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated,

the patient must start at the lowest dose and titrate up to avoid overdose (see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Starting Dose and Dose Titration).

- **Geriatrics**: In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Patients over the age of 65 years tended to titrate to slightly lower doses of FENTORA than younger patients and reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating FENTORA in elderly patients to provide adequate efficacy while minimizing risk (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

- **Patients with Hepatic and Renal Impairment**: FENTORA should be administered with caution to patients with hepatic or renal impairment. The influence of hepatic and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated, however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. After administration of FENTORA, impaired hepatic and renal function may both increase the bioavailability of swallowed fentanyl and decrease its systemic clearance, which could lead to increased and prolonged opioid effects. Therefore, caution should be taken during the titration process in patients with moderate or severe hepatic or renal impairment.

- **Special Risk Groups:** Fentanyl should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture (see 7 WARNINGS AND PRECAUTIONS, General).

4.4 Administration

- **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 sublingually. **Patients should not split the tablet.**

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

  The FENTORA tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 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.

  FENTORA may also be administered sublingually.

- **Disposal:**

  FENTORA should be kept in a safe place, out of the sight and reach of children before, during and after use. FENTORA should not be used in front of children, since they may copy these actions.

  FENTORA should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired FENTORA should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

5 OVERDOSAGE

- **Symptoms:** The manifestations of FENTORA overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effects being altered mental status, loss of consciousness, coma, hypotension, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

- **Immediate Management:** Immediate management of opioid overdose includes removal of the FENTORA tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as ventilatory and circulatory status.

- **Treatment of Overdosage (Accidental Ingestion) in the Opioid Non-Tolerant Person:** Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the product monograph of the individual opioid antagonist for details about such use.

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

- **General Considerations for Overdosage:** Management of severe FENTORA overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of respiratory depression or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

  Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Buccal or Sublingual	Fentanyl tablets containing: 100 micrograms fentanyl (as 157 mcg fentanyl citrate) 200 micrograms fentanyl (as 314 mcg fentanyl citrate) 400 micrograms fentanyl (as 628 mcg fentanyl citrate) 600 micrograms fentanyl (as 943 mcg fentanyl citrate) 800 micrograms fentanyl (as 1257 mcg fentanyl citrate)	citric acid, magnesium stearate, mannitol, sodium bicarbonate, sodium carbonate, sodium starch glycolate

FENTORA (fentanyl buccal/sublingual effervescent tablets) are flat-faced, round, beveled-edge in shape; are white in color; and are available in strengths of 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg fentanyl, as fentanyl citrate. Each tablet strength is marked with a unique identifier and is contained in a uniquely coloured carton/blister package, as described in the table below.

Dosage Strength	Debossing	Carton/Blister Package Colour
100 mcg	1	Blue
200 mcg	2	Orange
400 mcg	4	Sage green
600 mcg	6	Magenta (pink)
800 mcg	8	Yellow

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

Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is

debossed on one side with  , and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table above. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS.

General

It is important that the continuous opioid treatment used to treat the patient's persistent pain has been stabilized before starting FENTORA therapy. In cases where patients regularly experience more than 4 breakthrough pain episodes per day, increasing the opioid maintenance dose has to be considered before starting the titration process.

Patients should be instructed not to give FENTORA (fentanyl) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. FENTORA should be stored securely to avoid theft or misuse.

FENTORA should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking **FENTORA** as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of fentanyl can occur at particularly high doses. A fentanyl dose reduction or change in opioid may be required.

Addiction, Abuse and Misuse:

- Like all opioids, FENTORA is a potential drug of **abuse and misuse**, which can lead to overdose and death. Therefore, FENTORA should be prescribed and handled with caution.
- All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

- Opioids, such as FENTORA, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse and other mental health disorders including, but not limited to, major depression and anxiety. However, concerns about

abuse, addiction, and diversion should not prevent the proper management of pain.

FENTORA is intended for oral use only. The tablets should be placed between the cheek and gum, or under the tongue, and allowed to dissolve (see 4.4 DOSAGE AND ADMINISTRATION, Administration). Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Concomitant use with inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects (see 9 DRUG INTERACTIONS).

FENTORA is contraindicated for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics (see 2 CONTRAINDICATIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY section.

Cardiovascular

Fentanyl administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of FENTORA.

The use of FENTORA in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

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

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of FENTORA and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see 8 ADVERSE REACTIONS, and 4.2 DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

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

FENTORA is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of breakthrough cancer pain requiring opioid analgesia.

Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to FENTORA; extreme caution and awareness is warranted to mitigate the risk.

Driving and Operating Machinery

FENTORA may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned, accordingly. Patients should also be cautioned about the combined effects of fentanyl with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics~~,~~ and alcohol or gabapentinioids (gabapentin or pregabalin).

Endocrine

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal

function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal

FENTORA and other morphine-like opioids have been shown to decrease bowel motility. Fentanyl may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see 2 CONTRAINDICATIONS).

Neurologic

- Serotonin toxicity / Serotonin syndrome:
  Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with opioids, including FENTORA, particularly during combined use with other serotonergic drugs. (See 9 DRUG INTERACTIONS).

  Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:
  - Spontaneous clonus
  - Inducible clonus or ocular clonus with agitation or diaphoresis
  - Tremor and hyperreflexia
  - Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

  If concomitant treatment with FENTORA and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9 DRUG INTERACTIONS). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

- Interactions with Central Nervous System Depressants (including benzodiazepines, alcohol).
  Fentanyl should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), baclofen, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see 9 DRUG INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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 9 DRUG INTERACTIONS).

FENTORA should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2 CONTRAINDICATIONS, 8 ADVERSE REACTIONS, Sedation and 9 DRUG INTERACTIONS).

- Head Injury:
  The respiratory depressant effects of fentanyl, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, fentanyl may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, fentanyl must be used with extreme caution and only if it is judged essential (see 2 CONTRAINDICATIONS).

- Opioid-induced Hyperalgesia
  Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intraoperative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia) in the absence of disease

progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

Reproductive Health: Female and Male Potential

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8.5 ADVERSE REACTIONS, Post-Market Adverse Reactions).

Respiratory

- Respiratory Depression:
  Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, removal of the tablet if still in the mouth, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Fentanyl should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

  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 dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with FENTORA and following dose increases.

  Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

  To reduce the risk of respiratory depression, proper dosing and titration of FENTORA are essential (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and 4 DOSAGE AND ADMINISTRATION).

- Use in Patients with Chronic Pulmonary Disease:
  Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with FENTORA, as in these patients, even usual therapeutic doses of FENTORA may decrease respiratory drive to the point of apnea. The use of FENTORA is contraindicated in patients with acute or severe

bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2 CONTRAINDICATIONS).

- Sleep Apnea:
  Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance and 4.2 DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

7.1 Special Populations

7.1.1 Pregnant Women

Studies in humans have not been conducted. FENTORA crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgment of the physician, potential benefits outweigh the risks (see 7.1 WARNINGS AND PRECAUTIONS, Special Populations and 7.1.2 Labour, Delivery and Nursing Women).

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. **Neonatal Opioid Withdrawal Syndrome (NOWS)**, unlike opioid withdrawal syndrome in adults, can be life-threatening (see 8.5 ADVERSE REACTIONS, Post-Market Adverse Reactions) (see 3 SERIOUS WARNINGS AND PRECAUTIONS).

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

FENTORA is not recommended to be used in pregnant women unless, in the judgement of the

physician, the potential benefits outweigh the risks. If FENTORA was used during pregnancy, special attention to NOWS is warranted.

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

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

Fentanyl citrate was not teratogenic when administered to pregnant animals.

Studies were conducted assessing subcutaneous administration of fentanyl citrate to pregnant rats at doses of 0, 25, 50, or 100 mcg/kg/day from gestation Day 6 through 17 and to pregnant rabbits at doses of 50, 100, or 250 mcg/kg/day from gestation Day 6 through 18. The high dose in rats was approximately 1.2 times the human dose of 800 mcg per pain episode on a mg/m^2 basis. The high dose in rabbits was approximately 6 times the human dose of 800 mcg per pain episode on a mg/m^2 basis. There were no fentanyl-related external, visceral, or skeletal malformations or developmental variations noted (see 16 NON-CLINICAL TOXICOLOGY).

Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from Day 7 to 21, was not teratogenic. The high dose was approximately 6-times the human dose of 800 mcg per pain episode on a mg/m^2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg/day) to pregnant female rats from gestation Day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

7.1.2 Labour, Delivery and Nursing Women

Since opioids can cross the placental barrier and are excreted in breast milk, FENTORA is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if FENTORA is used in this population.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada,

the safety and efficacy of FENTORA in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The greater frequency of decreased hepatic, renal, or cardiac function, characteristic of the elderly, as well as concomitant disease and use of other drugs may impact the pharmacokinetics of FENTORA in this population. Caution should be exercised when dosing in the elderly. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see 4 DOSAGE AND ADMINISTRATION and 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Of the 358 patients with cancer in clinical studies of FENTORA, 76 (21%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating FENTORA in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression has occurred in the elderly when opioids were co-administered with other agents that can depress respiration.

7.1.5 Patients with Hepatic Impairment

FENTORA should be administered with caution to patients with liver dysfunction. The influence of liver impairment on the pharmacokinetics of FENTORA has not been determined. However, the clearance of intravenously administered fentanyl is decreased in hepatic disease due to alterations in metabolic clearance and plasma proteins (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

7.1.6 Patients with Renal Impairment

The influence of renal impairment on the pharmacokinetics of FENTORA has not been determined. FENTORA should be administered with caution to patients with renal impairment due to the potential for reduced renal excretion of fentanyl (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

7.1.7 Patients with Biliary/Pancreatic Disease

Fentanyl may cause spasm of the sphincter of Oddi and FENTORA should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in serum amylase concentration.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

Commonly observed adverse events seen with FENTORA (fentanyl buccal/sublingual effervescent tablet) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. These include, but are not limited to, nausea, vomiting, constipation, fatigue, headache, and dizziness.
The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest. Opioid side effects should be expected and managed accordingly.

An increase in fentanyl plasma concentration could lead to an increase in dose-related opioid adverse reactions. This may not be seen in opioid-tolerant patients who develop tolerance to opioid-related adverse reactions. If unacceptable dose-related opioid adverse reactions are observed, consider reducing the dosage. Adjust the dose of opioid to obtain an appropriate balance between management of pain and dose-related opioid adverse reactions (see 4 DOSAGE AND ADMINISTRATION)

8.2 Clinical Trial Adverse Drug Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

The safety of FENTORA has been evaluated in 2 double-blind, placebo-controlled studies and 1 12-month, open-label study which comprised 358 opioid-tolerant cancer patients with

breakthrough pain. Over a third (37%) of the patients received study drug for at least 3 months and 80 (22%) patients received study drug for at least 6 months.

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

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

Table 2 Adverse Events which Occurred During Titration at a Frequency of ≥ 5%

	Number (%) of patients[a]					
	Maximum Titration Dose of FENTORA					
System organ class MedDRA preferred term, n (%)	100 mcg (N=43)	200 mcg (N=36)	400 mcg (N=66)	600 mcg (N=65)	800 mcg (N=147)	Total (N=358[b])
Gastrointestinal disorders						
Nausea	5 (12)	6 (17)	15 (23)	15 (23)	18 (12)	59 (16)
Vomiting	1 (2)	2 (6)	4 (6)	9 (14)	3 (2)	19 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	2 (6)	6 (9)	3 (5)	6 (4)	20 (6)
Nervous system disorders						
Dizziness	4 (9)	2 (6)	12 (18)	21 (32)	24 (16)	64 (18)
Headache	1 (2)	3 (8)	5 (8)	8 (12)	11 (7)	28 (8)
Somnolence	1 (2)	2 (6)	6 (9)	8 (12)	4 (3)	21 (6)

[a] Patients are counted only once in each preferred term category and only once in each system organ class category.
[b] Successful dose was missing for 1 patient.
MedDRA=Medical Dictionary for Regulatory Activities.

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

Table 3 Adverse Events which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System organ class MedDRA preferred term, n (%)	Number (%) of patients[a] Successful Dose of FENTORA 100 mcg (N=21)	200 mcg (N=33)	400 mcg (N=53)	600 mcg (N=58)	800 mcg (N=74)	Total (N=239)
Blood and lymphatic system disorders						
Anemia	7 (33)	5 (15)	5 (9)	7 (12)	7 (9)	31 (13)
Neutropenia	1 (5)	2 (6)	1 (2)	5 (9)	6 (8)	15 (6)
Gastrointestinal disorders						
Nausea	9 (43)	5 (15)	18 (34)	20 (34)	19 (26)	71 (30)
Vomiting	8 (38)	7 (21)	11 (21)	13 (22)	12 (16)	51 (21)
Constipation	7 (33)	5 (15)	6 (11)	8 (14)	8 (11)	34 (14)
Abdominal pain	2 (10)	4 (12)	5 (9)	9 (16)	5 (7)	25 (10)
Diarrhoea	4 (19)	1 (3)	5 (9)	6 (10)	6 (8)	22 (9)
Stomatitis	1 (5)	3 (9)	4 (8)	2 (3)	3 (4)	13 (5)
Dyspepsia	1 (5)	1 (3)	3 (6)	2 (3)	5 (7)	12 (5)
General disorders and administration site conditions						
Fatigue	4 (19)	3 (9)	10 (19)	11 (19)	12 (16)	40 (17)
Oedema peripheral	8 (38)	4 (12)	4 (8)	8 (14)	8 (11)	32 (13)
Asthenia	4 (19)	5 (15)	2 (4)	6 (10)	10 (14)	27 (11)
Pyrexia	1 (5)	6 (18)	1 (2)	7 (12)	4 (5)	19 (8)
Infections and infestations						
Pneumonia	2 (10)	5 (15)	4 (8)	4 (7)	6 (8)	21 (9)
Urinary tract infection	0	2 (6)	2 (4)	5 (9)	6 (8)	15 (6)
Investigations						
Weight decreased	2 (10)	1 (3)	4 (8)	4 (7)	7 (9)	18 (8)
Metabolism and nutrition disorders						
Dehydration	4 (19)	0	4 (8)	7 (12)	9 (12)	24 (10)
Anorexia	2 (10)	2 (6)	6 (11)	5 (9)	8 (11)	23 (10)
Hypokalemia	0	2 (6)	0	2 (3)	9 (12)	13 (5)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	1 (3)	6 (11)	5 (9)	5 (7)	17 (7)
Back pain	3 (14)	0	3 (6)	7 (12)	3 (4)	16 (7)
Pain in extremity	1 (5)	0	2 (4)	4 (7)	4 (5)	11 (5)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)						
Cancer pain	3 (14)	1 (3)	3 (6)	4 (7)	1 (1)	12 (5)
Nervous system disorders						
Headache	2 (10)	1 (3)	5 (9)	9 (16)	14 (19)	31 (13)

	Number (%) of patients[a]					
	Successful Dose of FENTORA					
System organ class **MedDRA preferred term, n (%)**	**100 mcg (N=21)**	**200 mcg (N=33)**	**400 mcg (N=53)**	**600 mcg (N=58)**	**800 mcg (N=74)**	**Total (N=239)**
Dizziness	5 (24)	3 (9)	5 (9)	8 (14)	7 (9)	28 (12)
Psychiatric disorders						
Depression	2 (10)	1 (3)	7 (13)	7 (12)	7 (9)	24 (10)
Confusional state	4 (19)	1 (3)	2 (4)	4 (7)	5 (7)	16 (7)
Anxiety	0	2 (6)	3 (6)	6 (10)	4 (5)	15 (6)
Insomnia	2 (10)	1 (3)	5 (9)	2 (3)	4 (5)	14 (6)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (5)	5 (15)	1 (2)	8 (14)	3 (4)	18 (8)
Cough	2 (10)	0	3 (6)	5 (9)	6 (8)	16 (7)

[a] Preferred terms are sorted by descending order of incidence within system organ class. Patients are counted only once in each preferred term category and only once in each system organ class category.
MedDRA=Medical Dictionary for Regulatory Activities.

A small number of patients (n=11) with Grade 1 oral mucositis were included in clinical trials designed to support the safety of FENTORA. There was no evidence of excess toxicity in this subset of patients. Additionally, in an open-label study in opioid-tolerant patients with cancer, the safety profiles were found to be comparable in patients with (n = 8) and without (n = 8) oral mucositis (Grade 1) after administration of a single dose of FENTORA 200 mcg.

Application site reactions: In the 3 clinical trials, 9% of all patients exposed to FENTORA reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (3%), ulcer (3%), irritation (2%), and paresthesia (1%). Application site reactions tended to occur early in treatment, were self-limited and only resulted in treatment discontinuation for 2% of patients.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. (FENTORA is contraindicated for use in opioid non-tolerant patients.) Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in FENTORA clinical trials, whether related or not to fentanyl.

8.3 Less Common Clinical Trial Adverse Drug Reactions

The following adverse events were reported in the administration of FENTORA at a frequency between ≥ 1% and < 5%:

Blood and lymphatic system disorders: Leukopenia, lymphadenopathy, pancytopenia, thrombocytopenia

Cardiac disorders: Atrial fibrillation, tachycardia

Gastrointestinal disorders: Abdominal distension, abdominal pain upper, ascites, dry mouth, dyspepsia, dysphagia, food poisoning, gastrooesophageal reflux disease, gingival pain, glossodynia, mouth ulceration, oral mucosal discolouration, stomach discomfort

General disorders and administration site conditions: Application site irritation, application site pain, application site paraesthesia, application site ulcer, chest pain, chills, gait disturbance, oedema, pain

Hepatobiliary disorders: Jaundice

Infections and infestations: Bronchitis, cellulitis, gastroenteritis viral, influenza, nasopharyngitis, oral candidiasis, sepsis, sinusitis, tooth abscess, upper respiratory tract infection

Injury, poisoning and procedural complications: Contusion, fall, spinal compression fracture

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood glucose increased, breath sounds abnormal, haematocrit decreased, haemoglobin decreased, platelet count decreased

Metabolism and nutrition disorders: Decreased appetite, electrolyte imbalance, fluid retention, hypercalcaemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, oral intake reduced

Musculoskeletal and connective tissue disorders: Bone pain, chest wall pain, flank pain, muscle spasms, muscular weakness, myalgia, neck pain, osteoporosis, pain in extremity, shoulder pain

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Breast cancer, breast cancer metastatic, cancer pain, cervix carcinoma, colon cancer, colon cancer metastatic, lung cancer metastatic, lung neoplasm malignant, non-small cell lung cancer, pancreatic carcinoma

Nervous system disorders: Balance disorder, dysgeusia, hypoaesthesia, lethargy, migraine, neuropathy, neuropathy peripheral, paraesthesia, tremor, sedation

Psychiatric disorders: Disorientation, euphoric mood, hallucination, insomnia, nervousness

Renal and urinary disorders: Dysuria, renal failure

Respiratory, thoracic and mediastinal disorders: Dyspnoea exertional, epistaxis, haemoptysis, pharyngolaryngeal pain, pleural effusion, productive cough, pulmonary embolism, respiratory failure, wheezing

Skin and subcutaneous tissue disorders: Alopecia, cold sweat, erythema, hyperhidrosis, night sweats, pruritus, rash

Vascular disorders: Deep vein thrombosis, flushing, hot flush, hypertension, hypotension, pallor

8.5 Post-Market Adverse Reactions

Spontaneous reports received are consistent with the safety profile observed in clinical trials. The following additional adverse reactions have been identified during the post-marketing experience:

General disorders and administration site conditions: Drug tolerance, drug withdrawal syndrome, neonatal withdrawal syndrome, opioid use disorder.

Immune system disorders: hypersensitivity reactions (including rash, erythema, lip and face swelling, and urticaria).

Nervous system disorders: Loss of consciousness.

Psychiatric disorders: Delirium.

Respiratory, thoracic, and mediastinal disorders: Respiratory arrest

Androgen deficiency: 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• The concomitant use of FENTORA with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression. • FENTORA is contraindicated for use in patients who have received MAO inhibitors within 14 days. • The co-ingestion of alcohol with FENTORA should be avoided as it may result in dangerous additive effects, causing serious injury or death.

- Concomitant use of opioids with benzodiazepines, other central nervous system (CNS) depressants (including alcohol), may result in profound sedation, respiratory depression, coma, and death.

9.2 Drug Interactions Overview

CYP3A4 Inhibitors: Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when FENTORA is given concurrently with agents that affect CYP3A4 activity. The concomitant use of FENTORA with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving FENTORA who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done cautiously (see 7 WARNINGS AND PRECAUTIONS).

CYP3A4 Inducers: The concomitant use of FENTORA with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of FENTORA. Patients receiving FENTORA who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased FENTORA activity and the dose of FENTORA should be adjusted accordingly.

MAO Inhibitors: FENTORA is contraindicated for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics (see 2 CONTRAINDICATIONS).

Serotonergic Drugs: Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life threatening condition (see 7 WARNINGS AND PRECAUTIONS).

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, gabapentinoids such as pregabalin or gabapentin, baclofen, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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 7 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)).

9.3 Drug Behavioural Interactions

FENTORA should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects (see 7 WARNINGS AND PRECAUTIONS, General and Neurologic).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions

Drug Class [Examples]	Effect	Clinical Comment
Inhibitors of CYP3A4 [indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, cimetidine]	The concomitant use of FENTORA and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of FENTORA and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of FENTORA is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.	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.
CYP3A4 Inducers [barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone]	The concomitant use of FENTORA and CYP3A4 inducers can decrease the plasma concentration of fentanyl, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.	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.

Drug Class [Examples]	Effect	Clinical Comment
CNS Depressants [Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol, or gabapentinoids (gabapentin or pregabalin]	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.	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.
Serotonergic Drugs [Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5- HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (e.g. cyclobenzaprine), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)]	Co-administration of fentanyl with a serotonergic agent may increase the risk of serotonin syndrome, a potentially life threatening condition (see 7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome)	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue FENTORA if serotonin syndrome is suspected. FENTORA is contraindicated for use in patients who have received MAO inhibitors within 14 days (see 2 CONTRAINDICATIONS).
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics [Butorphanol, nalbuphine, pentazocine, buprenorphrine]	May reduce the analgesic effect of FENTORA and/or precipitate withdrawal symptoms.	Avoid concomitant use.

Drug Class [Examples]	Effect	Clinical Comment
Muscle Relaxants [Diazepam, cyclobenzaprine, methocarbamol, baclofen]	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.	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 [Amiloride, furosemide, hydrochlorothiazide, acetazolamide]	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs [amitriptyline, diphenhydramine, oxybutynin, olanzapine]	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.	Monitor patients for signs of urinary retention or reduced gastric motility when FENTORA is used concomitantly with anticholinergic drugs.

9.5 Drug-Food Interactions

Grapefruit and grapefruit juice, which are CYP3A4 inhibitors, may result in a potentially dangerous increase in fentanyl plasma concentrations.

9.6 Drug-Herb Interactions

The concomitant use of opioid analgesics with the sedative herbal supplements such as: St John's wort, valerian, kava and chamomile, may aggravate or alleviate central nervous system (CNS) depression. The analgesic effect of opioids may also be inhibited by ginseng.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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

Secondary actions include increase in the tone and decrease in the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipation typically seen with opioids.

- Analgesia: The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life). In opioid-naive individuals, analgesia occurs at blood levels of 1 to 2 ng/mL, while blood levels of 10-20 ng/mL would produce surgical anaesthesia and profound respiratory depression.

  In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of FENTORA should be individually titrated to achieve the desired effect.

- Central Nervous System**:** Fentanyl produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

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

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

- 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 is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

- Cardiovascular System: Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

- Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

- Immune System: *In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

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

  Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication.

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

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of FENTORA should be individually titrated to achieve the desired effect (see 4.2 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). 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.

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 4 DOSAGE AND ADMINISTRATION).

As with other opioids, tolerance and physical dependence may develop upon repeated administration of FENTORA and there is a potential for development of psychological dependence. Patients with a prior or family history of drug dependence/alcohol abuse are more at risk to develop psychological dependence (i.e. addiction) and abuse with opioid treatment (see 7 WARNINGS AND PRECAUTIONS, General).

10.3 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.

Table 5 Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90
T_{max} minute** (range)	45.0 (25.0 – 181.0)	40.0 (20.0 – 180.0)	35.0 (20.0 – 180.0)	40.0 (25.0 – 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
$T_{1/2}$, hr**	2.63 (1.47 – 13.57)	4.43 (1.85 – 20.76)	11.09 (3.44 – 20.59)	11.70 (4.63 – 28.63)

* Based on venous sampling.

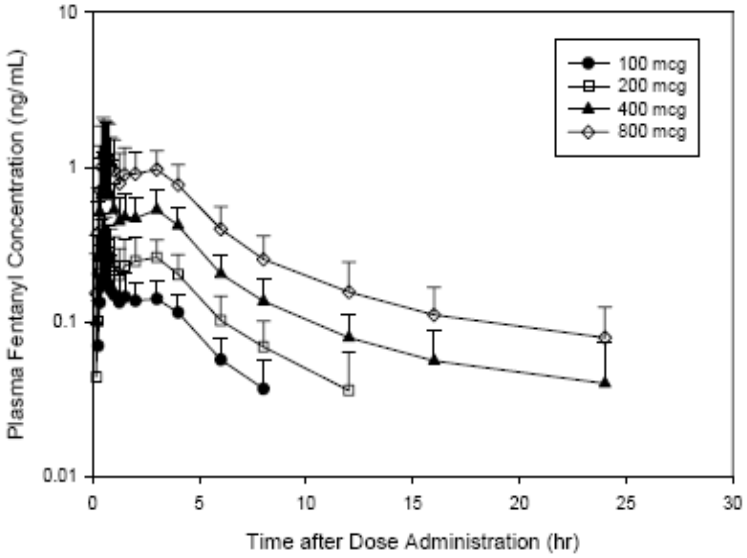
** Data for T_{max} presented as median (range)

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.

Mean pharmacokinetic parameters are presented in Table 5. Mean plasma concentration versus time profiles are presented in Figure 1.

Figure 1 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, except T_{max} where range was used) are presented in Table 6.

Table 6 Pharmacokinetic Parameters in Patients with Mucositis

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

Distribution:

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

Metabolism:

The metabolic pathways following buccal administration of FENTORA have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations

results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active.

Elimination:

Disposition of fentanyl following buccal administration of FENTORA has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

Special Populations and Conditions

- **Pediatrics:** A pediatric indication has not been authorized by Health Canada.

- **Geriatrics:** No formal study has been performed to assess FENTORA pharmacokinetics in elderly subjects or patients. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

- **Sex:** Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.
  Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 20% and 17% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

- **Ethnic Origin:** The pharmacokinetic effects of ethnic origin 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 non-Japanese subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to non-Japanese subjects (57.4 kg versus 73 kg).

- **Hepatic Impairment:** Insufficient information exists to make recommendations regarding the use of FENTORA in patients with impaired hepatic function. Fentanyl is metabolized primarily in the liver via human cytochrome P450 3A4 isoenzyme system.

If FENTORA is used in patients with hepatic impairment, it should be used with caution due to the hepatic metabolism of fentanyl.

- **Renal Impairment:** Insufficient information exists to make recommendations regarding the use of FENTORA in patients with impaired renal function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in patients with renal impairment, it should be used with caution due to the renal excretion of fentanyl.

11 STORAGE, STABILITY AND DISPOSAL

FENTORA (fentanyl buccal/sublingual effervescent tablets) is supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in FENTORA can be fatal to a child. **Patients and their caregivers must be instructed to keep FENTORA out of the reach of children.**

Store in original package at 20 to 25ºC, with excursions permitted between 15° and 30°C, until ready to use.

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

FENTORA should be kept in a safe place, out of the sight and reach of children before, during and after use. FENTORA should not be used in front of children, since they may copy these actions.

FENTORA should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired FENTORA should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product (see 11 STORAGE STABILITY AND DISPOSAL).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

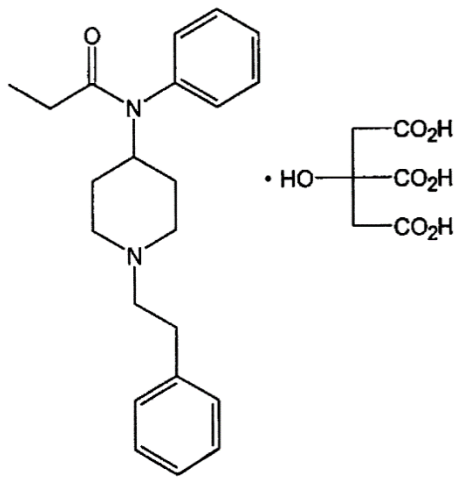
Drug Substance

Proper name: Fentanyl citrate

Chemical name: N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1)

Molecular formula and molecular mass:
$C_{22}H_{28}N_2O \cdot C_6H_8O_7$
Free base: 336.5
Citrate salt: 528.6

Structural formula:



Physicochemical properties of fentanyl citrate, including solid state: Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The pKa of the tertiary nitrogens are 7.3 and 8.4.

Product Characteristics:

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 absorption through the membrane (at a higher pH) of fentanyl through the buccal mucosa.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%)
099-14	A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study of fentanyl citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients	fentanyl citrate tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg Placebo Buccal tablets for oral transmucosal administration Titration period was up to 21 days Double-blind treatment period was up to 21 days	123	58.0 ± 12.58 (SD) years (range 27 to 87 years)	Male 67 (54) Female 56 (46)
3039	A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of fentanyl citrate in Opioid-Tolerant Patients With Cancer and Breakthrough Pain	fentanyl citrate tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg Placebo Buccal tablets for oral transmucosal administration Open-label dose titration period was approximately 7 days Double-blind treatment was period was up to 21 days	125	54.9 ± 10.92 (SD) years (range 29 to 79 years)	Male 48 (38) Female 77 (62)

099-15	Phase 3, Multi-center, Open Label, Long-term Study of fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid Tolerant Cancer Patients	fentanyl citrate tablets 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg Buccal tablets for oral transmucosal administration Titration period was ≤21 days Maintenance period was ≥12 months	232	55.3 ± 12.7 (SD) years	Male 110 (47) Female 122 (53)

The efficacy of FENTORA was demonstrated in two double-blind, placebo-controlled, cross-over studies in opioid tolerant patients with cancer and breakthrough pain.

In these studies, 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 measured at 15, 30, 45 and 60 minutes for Study 1 and at 5, 10, 15, 30, 45, 60, 90, and 120 minutes for Study 2, after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure in Study 1 and the sum of differences in pain intensity scores at 5 through 60 minutes from baseline ($SPID_{60}$) was the primary efficacy measure in Study 2.

14.2 Study Results

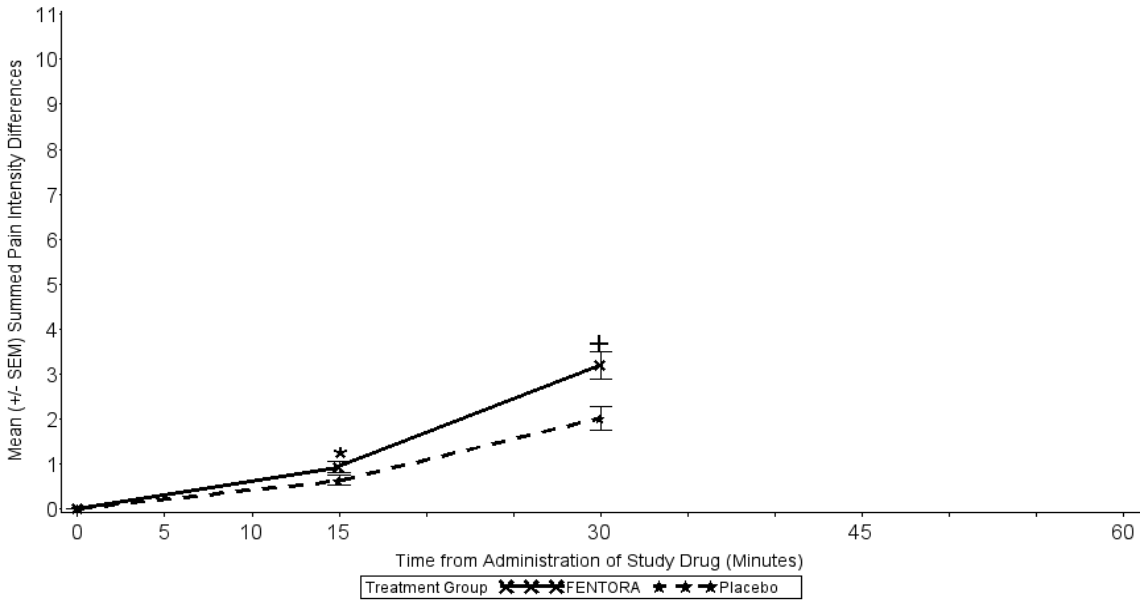
Sixty-five percent (65%) of patients in Study 1 and 70% of patients in Study 2, who entered the respective study, achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 7. The median dose for both studies was 400 mcg.

Table 7 Successful Dose of FENTORA Following Initial Titration

FENTORA Dose	Study 1 (N=80) n (%)	Study 2 (N=87) n (%)
100 mcg	13 (16)	7 (8)
200 mcg	11 (14)	10 (12)
400 mcg	21 (26)	16 (18)
600 mcg	10 (13)	24 (28)
800 mcg	25 (31)	30 (34)

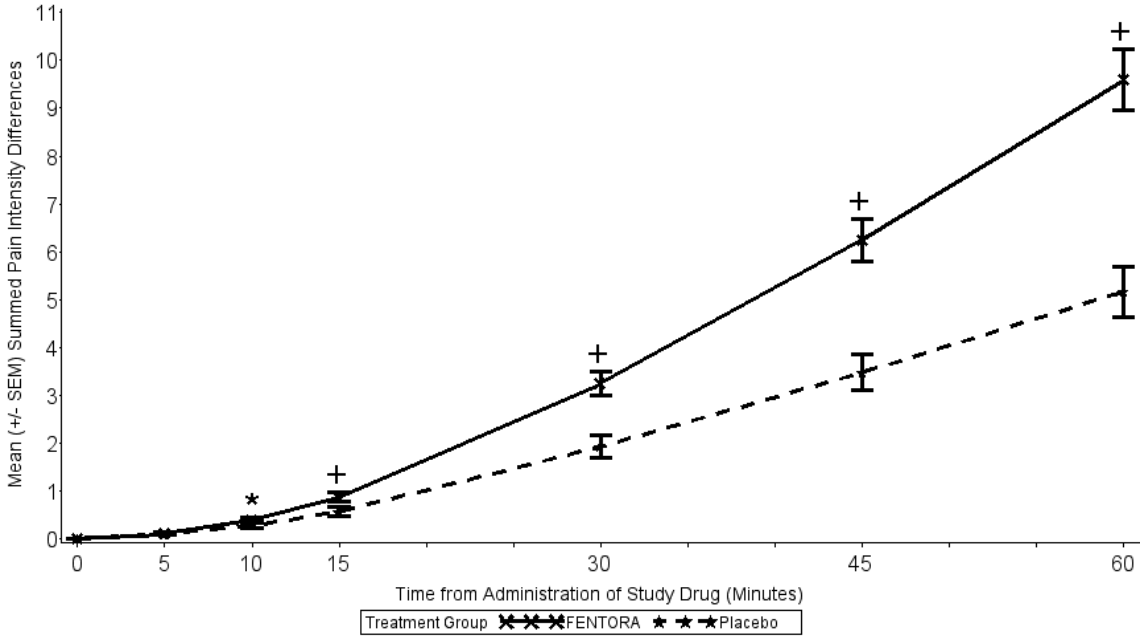
For Study 1, the LS mean (SE) $SPID_{30}$ for FENTORA-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18), and for Study 2, the LS mean (SE) $SPID_{60}$ for FENTORA-treated episodes was 9.8 (0.26) while for placebo-treated episodes it was 5.0 (0.38).

Figure 2 Mean Summed Pain Intensity Differences (SPID) at Each Time Point during the Double-Blind Treatment Period (Study 1)



* p<0.01 FENTORA versus placebo, in favor of FENTORA, by analysis of variance
\+ p<0.0001 FENTORA versus placebo, in favor of FENTORA, by analysis of variance

Figure 3 Mean Summed Pain Intensity Differences (SPID) at Each Time Point during the Double-Blind Treatment Period (Study 2)



* p<0.01 FENTORA versus placebo, in favor of FENTORA, by analysis of variance
\+ p<0.0001 FENTORA versus placebo, in favor of FENTORA, by an analysis of variance

Statistically significant improvement in pain intensity difference was seen with FENTORA versus placebo as early as 15 minutes (earliest time point measured) in Study 1 and as early as 10 minutes in Study 2. These differences continued to be significant at each subsequent time point in each individual study.

The efficacy and safety of FENTORA was further supported in a long-term, open-label study in opioid-tolerant patients with cancer and breakthrough pain, in which patients were treated for up to 23 months.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The toxicity profile of fentanyl by various routes of administration is well-established.

General Toxicology

Acute toxicity studies showed that the fentanyl mortality dose response curve in mice was biphasic following both subcutaneous and intravenous dosing. The mechanism for this biphasic response is not known, but the mortality observed at the low end of the dose-response curve was considered to be associated with respiratory depression. Median lethal fentanyl doses (LD_{50}) following intravenous and subcutaneous administration of fentanyl to mice were 11.2 and 62 mg/kg, respectively.

In rats, the mean acute LD_{50} following intravenous administration was calculated to be 6 mg/kg, following subcutaneous administration was calculated to be 3.1 to 12 mg/kg and following oral administration was calculated to be 18 mg/kg.

In dogs, an extensive investigation of the cardiovascular, neurological and metabolic side effects was evaluated using 8 opioids. The findings, which applied to all opioids tested, indicated an inverse relationship between analgesic potency and hemodynamic, neurological and metabolic toxicity. In general, the more potent and shorter acting the opioid, the higher the margin of safety.

A number of repeat-dosing studies, ranging in duration from 2 to 13 weeks, using fentanyl by parenteral routes in mice, rat, rabbit and dog have been reported. In rats, deaths occurred following oral doses of 10 mg/kg/day or more or at intramuscular doses of 0.1 or 0.4 mg/kg/day. The main findings in the majority of these studies were adverse effects on CNS (decreased activity, impaired righting reflex, prostration) and weight gain, and there was no clear-cut evidence to suggest direct organ or tissue toxicity although the range of parameters examined was limited. Fentanyl was well tolerated in rabbits in transcutaneous route studies of up to 90 days' duration and no deaths occurred in dogs administered the drug by the intramuscular route, at a maximum dose of 0.4 mg/kg/day for 4 weeks. In FVB/N mice, dermal application up to 500 mcg/mouse for 28 days (in support of dose selection for a 26-week carcinogenicity study in transgenic mice, Tg.AC strain) resulted in hyperactivity and slightly lower body weight gains relative to concurrent control values.

Carcinogenicity

A 26-week Tg.AC transgenic mouse dermal carcinogenicity study was conducted with fentanyl. The mice were treated with daily dermal applications of 5, 15 or 50 mcg/dose/day of fentanyl in acetone. A positive control group was included and was dosed dermally with 1.25 mcg TPA in acetone, three times per week. There were no treatment-related increases in the incidence of dermal papilloma formation at the site of application, and no increase in the occurrence of neoplastic lesions. The positive control produced the expected significant increase in the

incidence of dermal papillomas at the site of application, thereby validating the results of this 26-week dermal carcinogenicity study.

A 104-week subcutaneous carcinogenicity study in rats was conducted with fentanyl citrate. Dose levels evaluated in this study were 0, 12.5, 25, and 50 mcg/kg/day for male rats, and 0, 25, 50 and 100 mcg/kg/day for female rats (dose levels expressed as fentanyl base). Fentanyl did not produce any microscopic findings that were indicative of oncogenic potential following lifetime exposure.

Genotoxicity

Fentanyl citrate was evaluated in a standard battery of genotoxicity studies, an in vitro bacterial reverse mutation assay, an in vitro mammalian cell (L5178Y mouse lymphoma cells) mutagenicity assay, and an in vivo mouse micronucleus assay.

In the in vitro mutation studies, there was no evidence of mutagenicity in *Salmonella typhimurium* test strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* test strain WP2 *uvrA*, in the presence and absence of metabolic activation (Aroclor-induced rat liver S9).

Fentanyl was negative for induction of micronucleated polychromatic erythrocytes (MNPCE) in an in vivo mouse bone marrow cytogenetic assay. In vitro and in vivo genotoxicity studies did not show any evidence for a genotoxic potential for fentanyl.

Reproductive and Developmental Toxicity

Developmental and reproductive toxicity studies consisting of a fertility and general reproductive performance study in rats, studies to assess embryo-fetal development in rats and rabbits, and a study in rats to determine pre- and postnatal development, including an evaluation of behavior, learning and reproductive function in the F_1 offspring have been performed.

In the fertility and early embryonic development study in rats where treated male rats were mated with untreated female rats and treated female rats were mated with untreated males, a male mediated effect was observed in the untreated females mated with males given subcutaneous doses of 300 mcg/kg/day for 28 days prior to mating. The observed effects in these untreated females included significant decreases in implantation sites, significant increases in pre-implantation loss and decreases in viable embryos. These effects were related to severe changes in sperm parameters including a significant decrease in the percentage of mobile sperm and sperm concentrations, and a significant increase in the percentage of abnormal sperm. These effects were considered to be indirect effects of fentanyl treatment in these male rats. Due to the marked sedation noted in these males, it is likely that the testis was pushed into the inguinal canal, thereby affecting the temperature of the testis leading to adverse effects on spermatogenesis in these males. No reproductive effects were seen in

treated females mated with untreated males.

Embryo-fetal developmental toxicity studies were also conducted in rats and rabbits. Although the expected exaggerated pharmacological effects of fentanyl were observed in both studies, there were no fentanyl-related malformations or developmental variations observed in pregnant female rats at subcutaneous doses up to 100 mcg/kg/day, or in pregnant rabbits at subcutaneous doses up to 250 mcg/kg/day, when administered during the period of organogenesis.

In a pre- and post-natal developmental toxicity study which evaluated the effect of fentanyl citrate on the pregnant/lactating female rat and on development of the conceptus and offspring following exposure of the female from implantation through weaning, mortality and exaggerated pharmacological effects were observed at doses of 100 and 400 mcg/kg/day. Based upon the significant maternal toxicity observed at 400 mcg/kg/day, several adverse effects were observed in the F_1 litters. The number of live pups/litter was significantly decreased on post-natal day 4 at 400 mcg/kg/day. Clinical signs observed in these F_1 pups during the lactation included decreased activity, skin cold to touch, and moribundity. In this group, pup body weights were lower throughout lactation, and continued to be lower throughout the premating, mating and gestation period. In the 400 mcg/kg/day group, a delay in static righting reflex and eye opening, and reduced auditory response were observed. Sexual maturation was delayed in these high-dose pups. Motor activity parameters were also affected by treatment with 400 mcg/kg/day. No effects on reproductive and fertility parameters were observed in the F_1 pups, although the mean implantation sites were reduced in the F_1 pups from the 400 mcg/kg/day group.

Test article-related clinical signs in F_1 pups during the lactation period consisted of decreased activity, skin cold to touch, and moribundity. Pup body weights by sex and both sexes combined were significantly reduced throughout the lactation period (PND 0-21) and continued to be lower throughout the premating, mating, and gestation period at 400 mcg/kg/day. Male pup body weights were significantly lower on PND 4 (pre- and post-culling) at 100 mcg/kg/day. A test article-related delay in static righting reflex and eye opening and reduced auditory response were observed in pups at 400 mcg/kg/day. Additionally, vaginal opening and preputial separation were significantly delayed at 400 mcg/kg/day. Some motor activity parameters were also affected at 400 mcg/kg/day. No effect on F_1 reproductive and fertility parameters were seen in any of the dosing groups; however, mean implantation sites per animal were significantly reduced at 400 mcg/kg/day. A dose-related systemic exposure of pregnant female rats to fentanyl and norfentanyl was demonstrated following once-daily subcutaneous administration of 25, 50, 100 or 400 mcg/kg/day fentanyl base for up to approximately 5 weeks (i.e. from GD 6 to LD 20). Based on the results of this pre- and postnatal developmental toxicity study, the no-observed-adverse-effect level (NOAEL) for maternal, reproductive, and developmental toxicity was considered to be 50 mcg/kg/day.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{N}FENTORA™
Fentanyl Buccal/Sublingual Effervescent Tablets

Read this carefully before you start taking **FENTORA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FENTORA**.

Serious Warnings and Precautions

- Do NOT use FENTORA unless you are regularly using another opioid pain medicine continuously for your cancer pain and your body is used to these medicines (this means you are opioid tolerant). You can ask your healthcare professional if you are opioid tolerant.
- Even if you take FENTORA as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk for opioid addiction, abuse, and misuse, you should speak to your healthcare professional.
- Life-threatening breathing problems can happen while taking FENTORA, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- You should never give anyone your FENTORA. They could die from taking it. If a person has not been prescribed FENTORA, taking even one dose can cause a fatal overdose. This is especially true for children and for an adult who is not already taking opioids continuously.
- In an emergency, try to remove FENTORA from the mouth.
- If you stop taking your regular opioid pain medicine for your cancer pain, you must stop using FENTORA. You may no longer be opioid-tolerant. Talk to your healthcare professional about how to treat your pain.
- You or a family member should call your healthcare professional or get emergency medical help immediately if you have trouble breathing, drowsiness with slow breathing, slow shallow breathing (little chest movement with breathing) or feel faint, dizzy, confused, or have other unusual symptoms. These can be symptoms of an overdose with FENTORA. Your dose of FENTORA may be too high for you. These symptoms may lead to serious problems or death if not treated immediately. If you have any of the above symptoms, do not take another dose of FENTORA.
- Use FENTORA exactly as prescribed by your healthcare professional.
    - You must begin treatment with FENTORA at the lowest dose of 100 mcg.
    - You must not use more than ONE dose of FENTORA for each episode of breakthrough cancer pain.
    - You must wait at least 4 hours before treating a new episode of breakthrough pain with FENTORA.
    - You must not treat more than 4 episodes of breakthrough pain per day. Talk to your healthcare professional 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 changed.
- Do not switch from FENTORA to other medicines that contain fentanyl without talking with your healthcare professional. 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 professional will prescribe a starting dose of FENTORA that may be different than other fentanyl containing medicines you may have been taking.

- If you took FENTORA while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
  - has changes in their breathing (such as weak, difficult or fast breathing),
  - is unusually difficult to comfort ,
  - has tremors (shakiness),
  - has increased stools, sneezing, yawning, vomiting, or fever.

  Get immediate medical help for your baby.
- Keep FENTORA in a safe place away from children and pets. Do not use FENTORA in front of children.
- Taking FENTORA with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

What is FENTORA used for?
FENTORA is used in adults (18 years of age and older) to manage sudden bursts of pain described as “breakthrough pain” in adults with cancer who are already taking other opioid pain medicines regularly 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.

How does FENTORA work?
FENTORA is a painkiller belonging to the class of drugs known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in FENTORA?
Medicinal ingredient: Fentanyl citrate.
Non-medicinal ingredients: Citric acid, magnesium stearate, mannitol, sodium bicarbonate, sodium carbonate, and sodium starch glycolate.

FENTORA comes in the following dosage forms:
Buccal/sublingual effervescent tablets (a tablet that you place between your gum and cheek or under the tongue): 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg of fentanyl (as fentanyl citrate). Each tablet strength comes in a box and blister pack with a different colour, as shown below:

Tablet Strength	Box and Blister Colour
100 mcg	Blue
200 mcg	Orange
400 mcg	Sage green
600 mcg	Magenta (pink)
800 mcg	Yellow

Do not use FENTORA if:

- your healthcare professional did not prescribe it for you.
- you are not taking other opioid pain medicines for your cancer pain. Your body must already be used to taking opioid pain medicine when you take FENTORA.
- you are allergic to fentanyl citrate, other opioids, or any of the other ingredients in FENTORA.
- you have severe asthma, trouble breathing, or other lung problems.
- you have any heart problems.
- you have bowel blockage or narrowing of the stomach or intestines.
- you have a condition where the bowel does not work properly (ileus) or have severe pain in your abdomen.
- you have increased pressure in your skull or have a head injury.
- you have epilepsy (seizures) or a history with epilepsy.
- you suffer from alcoholism or alcohol withdrawal.
- you are taking or have taken within the past 2 weeks a monoamine oxidase inhibitor (MAOi) used to treat depression (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).
- you are going to have a surgery or operation or have had a surgery in the last 24 hours.
- you have severe central nervous system (CNS) depression (nervous system slows down).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FENTORA. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse.
- have kidney, liver, or lung problems.
- have been told you are at risk of having heart problems or seizures.
- have low blood pressure.
- have a history of sleep apnea.
- have had problems with your mood (such as depression or anxiety), hallucinations, or

other mental health problems.
- suffer from migraines.
- suffer from chronic or severe constipation.
- have problems with your thyroid, adrenal or prostate gland.
- have, or had in the past, hallucinations or other severe mental health problems.
- are pregnant, planning to become pregnant, or are in labour.
- are breastfeeding or planning to breastfeed.
- have a sleep disorder which causes pauses in breathing or shallow breathing while sleeping (sleep apnea).
- are planning on drinking alcohol. Drinking alcohol while taking FENTORA may cause dangerous side effects, including death. Do NOT drink alcohol while taking FENTORA.
- have a condition that causes weakness or frailty.

Other warnings you should know about:

Drug addiction, dependence and tolerance: Like any opioid, FENTORA may cause mental and physical dependence. Fentanyl citrate also has the potential to cause addiction. There are important differences between physical dependence and addiction. Tolerance means that, over time, a higher dose may be needed to get the same level of pain relief. It is important that you talk to your healthcare professional if you have questions or concerns about addiction, physical dependence, or tolerance. Your healthcare professional should prescribe and administer FENTORA with the same degree of caution appropriate to the use of other oral opioid medications. It is not recommended to use these products for a long period of time.

Pregnancy, breastfeeding, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. FENTORA can then cause life-threatening breathing problems in your unborn baby or breastfeeding infant. Your healthcare professional will determine if the benefits of using FENTORA outweigh the risks to your unborn baby or breastfeeding infant.

If you are pregnant and are taking FENTORA, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your healthcare professional will monitor and guide you on how to slowly stop taking FENTORA. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to FENTORA. FENTORA can cause:
- drowsiness,
- dizziness, or
- lightheadedness.

This can usually occur after you take your first dose and when your dose is increased. Taking FENTORA with other medicines that affect your nervous system, including:

- other opioids,
- phenothiazine (used to treat mental health problems and prevent vomiting during chemotherapy),
- sedatives and hypnotics (used to cause relaxation and help you sleep),
- gabapentin (used to prevent seizures),
- pregabalin (used to treat nerve pain), and
- alcohol, which can make these side effects worse.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting;
- feeling tired, weak or dizzy;
- decreased appetite.

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your healthcare professional may do tests, give you another medication, and slowly take you off FENTORA.

Serotonin toxicity (also known as serotonin syndrome): FENTORA can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin toxicity if you take FENTORA with certain anti-depressants, migraine or muscle relaxants medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual function/reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Sleep apnea: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your healthcare professional if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

Worsened pain: Taking opioids for pain can sometimes have the unintended effect of making

your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your healthcare professional if you notice a change like this in your pain while you are taking FENTORA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking FENTORA with the following medicines can cause serious side effects, including breathing problems that can lead to death:

- cimetidine, used to treat heart burn and ulcers.
- nefazodone, an antidepressant.
- aprepitant, a medicine used to prevent vomiting.
- medicines used to treat HIV/AIDS (e.g. indinavir, nelfinavir, ritonavir, saquinavir).
- medicines used to treat fungal infections (e.g. itraconazole, ketoconazole, fluconazole).
- antibiotics used to treat bacterial infections (e.g. erythromycin, clarithromycin, telithromycin, rifabutin, rifampin).
- calcium channel blockers, used to treat high blood pressure and chest pain (e.g. diltiazem, verapamil).
- Monoamine Oxidase Inhibitors (MAOi), used to treat depression. Do NOT take FENTORA with MAOi's or if you have taken an MAOi in the last 14 days.
- benzodiazepines, medicines used to help you sleep or that help reduce anxiety (e.g. diazepam, lorazepam, alprazolam).
- alcohol, including prescription and non-prescription medications that contain alcohol. Do NOT drink alcohol while you are taking FENTORA. It can lead to:
    - drowsiness,
    - unusually slow or weak breathing,
    - serious side effects or,
    - a fatal overdose.
- antiepileptics, used to treat and prevent seizures (e.g., gabapentin, carbamazepine, phenytoin, oxcarbazepine, phenobarbital).
- pregabalin (used to treat nerve pain).
- other sedative drugs which may enhance the drowsiness caused by FENTORA.
- other opioid analgesics, medicines used to treat pain (e.g. butorphanol, nalbuphine, pentazocine, buprenorphrine).
- general anesthetics (medicines used during surgery).

- antidepressants, for depression and mood disorders (e.g. amitriptyline).
- medicines used to treat serious mental health problems such as schizophrenia (e.g. olanzapine).
- antihistamines, medicines used to treat allergies (e.g. diphenhydramine).
- anti-emetics (medicines used for the prevention of vomiting).
- medicines known as muscle relaxants used to treat muscle spasms and back pain (e.g. diazepam, cyclobenzaprine, methocarbamol, baclofen).
- St. John's Wort, an herbal medicine used to treat depression.
- grapefruit juice.

The following may also interact with FENTORA:

- medicines used to treat migraines (e.g. triptans).
- diuretics or "water pills" used to lower high blood pressure (e.g. amiloride, furosemide, hydrochlorothiazide, acetazolamide).
- medicines used to treat HIV/AIDS (e.g. efavirenz, nevirapine).
- medicines used to treat diabetes (troglitazone, pioglitazone).
- glucocorticoids, steroid medicines used to reduce inflammation.
- modafinil, used to reduce sleepiness in sleep apnea and other sleep disorders.
- oxybutynin, used to treat bladder problems such as overactive bladder.
- herbal supplements such as valerian, kava, chamomile and ginseng.

How to take FENTORA:

- Take FENTORA exactly as directed by your healthcare professional.
- **Do NOT split, suck, chew, or swallow FENTORA tablets. You will get less relief for your breakthrough cancer pain. Use FENTORA tablets whole.**
- Review your pain regularly with your healthcare professional to determine if you still need FENTORA. Be sure to use FENTORA only for the condition for which it was prescribed.
- If your pain increases or you develop any side effect as a result of taking FENTORA, tell your healthcare professional immediately.
- Wait 30 minutes after using FENTORA. If any FENTORA tablet is left in your mouth, you may drink a glass of water to help you swallow the left-over medicine.

Usual Dose:

All patients MUST begin treatment using one 100 mcg FENTORA tablet.

Your dose is tailored/personalized just for you. Be sure to follow your healthcare professional's dosing instructions exactly. Do not increase or decrease your dose without talking to your healthcare professional. Your healthcare professional will instruct you on how to safely increase your dose until you reach a dose that gives you enough pain relief.

Your healthcare professional will give you a prescription to treat up to four breakthrough pain episodes per day by using the right dose.

You must not use more than one dose of FENTORA for each episode of breakthrough cancer pain.

- If your breakthrough pain does not get better after the single dose of FENTORA, call your healthcare professional for instructions. **Do not use another dose of FENTORA for the same episode of breakthrough pain.**

Wait at least **4** hours before treating a new episode of breakthrough cancer pain with FENTORA.

- Take only one dose of FENTORA for an episode of breakthrough pain. You must wait **4** hours from the time of that dose to take another dose of FENTORA for a **new** episode of breakthrough pain.

It is important for you to keep taking your opioid pain medicine regularly while using FENTORA.

Talk to your healthcare professional if your dose of FENTORA does not relieve your breakthrough cancer pain. Your healthcare professional will decide if your dose of FENTORA

needs to be changed. Do not skip to a higher dose unless instructed to do so by your healthcare professional.

Do not treat more than 4 breakthrough pain episodes per day with FENTORA. Talk to your healthcare professional if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your regular opioid pain medicine may need to be changed.

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.

FENTORA Dosing Instructions:

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

FENTORA comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA tablet.

- **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. See **Figure 1**
- Bend the blister unit along the line where indicated. The product strength of your FENTORA tablets will be printed in the box below and in **Figure 1**:

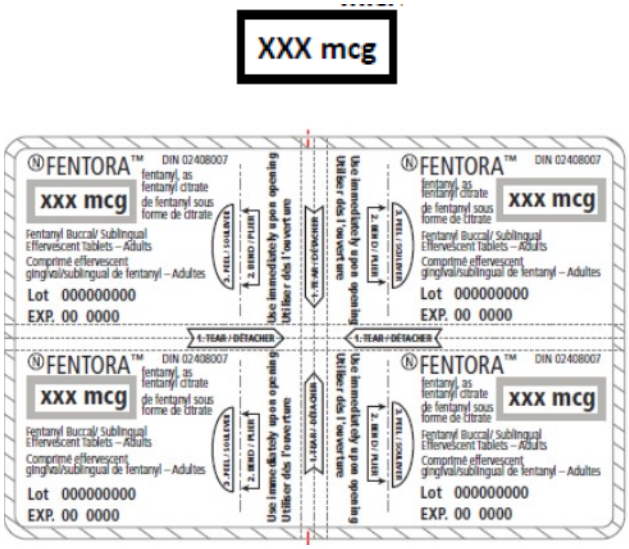


Figure 1

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

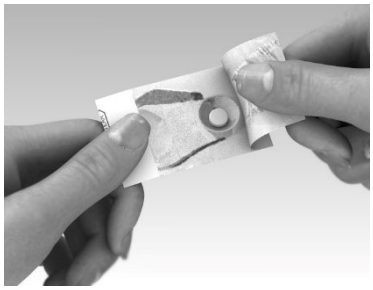


Figure 2

- **Do not push the tablet** through the foil on the blister unit because this could damage the tablet.
- When removed from the blister unit, FENTORA tablet must be used right away.
- Do NOT split the FENTORA tablet. **Use FENTORA tablets whole**.
- You can place a FENTORA tablet in your mouth two ways:
    1. **Buccal:** above a back molar tooth between the upper cheek and gum (see **Figure 3**).

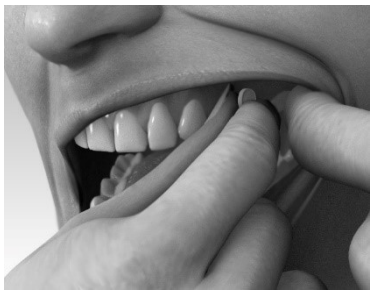


Figure 3

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

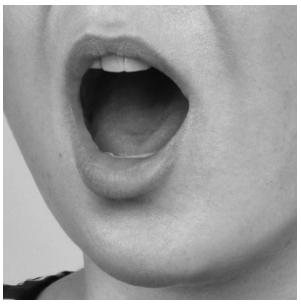


Figure 4a

Figure 4b

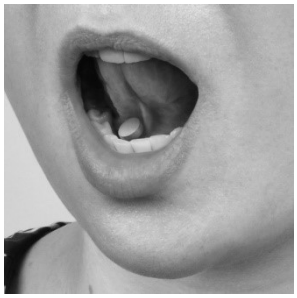


Figure 4c

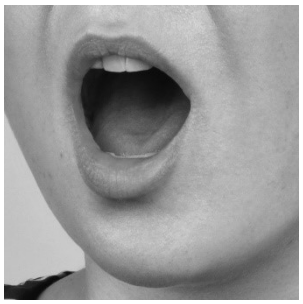


Figure 4d

- **Leave the tablet in place until it dissolves.** A FENTORA tablet generally takes 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 professional. Your healthcare professional will tell you what to do. Do NOT split the tablet.
- **Do NOT split, suck, chew or swallow FENTORA tablets.** You will get less relief for your breakthrough cancer pain.

Stopping your Medication

If you have been taking FENTORA for more than a few days you should not stop taking it all of a sudden. Your healthcare professional will monitor and guide you on how to slowly stop taking FENTORA. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches;
- diarrhea;
- goosebumps;
- loss of appetite;
- nausea;
- feeling nervous or restless;
- runny nose;
- sneezing;
- tremors or shivering;
- stomach cramps;
- rapid heart rate (tachycardia);
- having trouble sleeping;
- an unusual increase in sweating;
- heart palpitations;
- an unexplained fever;
- weakness;
- yawning.

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking FENTORA.

Refilling your Prescription for FENTORA:

A new written prescription is required from your healthcare professional each time you need more FENTORA. Therefore, it is important that you talk to your healthcare professional before your current supply runs out.

Only obtain prescriptions for this medicine from the healthcare professional in charge of your treatment. Do not seek prescriptions from other healthcare professionals unless you switch to another healthcare professional for your pain management.

Overdose:
Signs of overdose may include:

- unusually slow or weak breathing,
- dizziness,
- confusion,
- extreme drowsiness,
- coma,
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter).

In cases of possible overdose try to remove any FENTORA tablets still remaining in the mouth.

If you think you, or a person you are caring for, have taken too much FENTORA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FENTORA?
These are not all the possible side effects you may have when taking FENTORA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Drowsiness;
- Insomnia;
- Dizziness;
- Fainting;
- Nausea, vomiting, or a poor appetite;
- Dry mouth;
- Headache;
- Problems with vision;
- Weakness, uncoordinated muscle movement;
- Itching;
- Sweating;
- Constipation. Talk with your healthcare professional about ways to prevent constipation when you start using FENTORA;
- Low sex drive, impotence (erectile dysfunction), infertility.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: itchy, red, painful, and irritated or swollen skin (rash), outbreak of pale red bumps or welts on the skin that appear suddenly (hives), swelling of the face, lips, tongue or throat, difficulty swallowing, or difficulty breathing.			√
Bowel blockage (impaction): abdominal pain, severe constipation, nausea.			√
Fast, slow or irregular heartbeat: heart palpitations.		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness.	√		
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory depression: slow, shallow or weak breathing or shortness of breath.			√
Serotonin toxicity (also known as serotonin syndrome): a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38°C), or rigid muscles.			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering,		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
cold and clammy skin, body aches, loss of appetite, sweating.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store FENTORA in original package between 15° and 30°C, until ready to use. Keep in a dry place and protected from moisture.
- Keep FENTORA in the original blister unit. FENTORA should be used immediately after opening the child-resistant package. Do NOT remove FENTORA from its blister packaging for storage in a temporary container, such as a pill box.
- Do NOT use if the blister package has been tampered with.
- Keep FENTORA under lock, out of sight and reach of children and pets.
- Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes FENTORA, get emergency help right away.
- Keep unused or expired FENTORA in a secure place to prevent theft, misuse or accidental exposure.

Disposal: To prevent accidental ingestion, and to reduce the chance of children taking the medication, it is important to properly dispose of any excess FENTORA as soon as it is no longer needed. FENTORA should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about FENTORA:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's (Teva Canada Limited) website (http://www.tevacanada.com), or by calling 1-855-513-8382.

This leaflet was prepared by Teva Canada Innovation for Teva Canada Limited.

Last Revised: June 27, 2023