NFENTORA™

Fentanyl Buccal/Sublingual Effervescent Tablets
100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg fentanyl as fentanyl citrate

Opioid Analgesic

Guide for Prescribers

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

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

INDICATIONS AND CLINICAL USE[1]

FENTORA 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.

All patients starting treatment with FENTORA must begin with titration from the 100 mcg dose.

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 postoperative pain, including headache/migraine, dental pain or use in the emergency room.

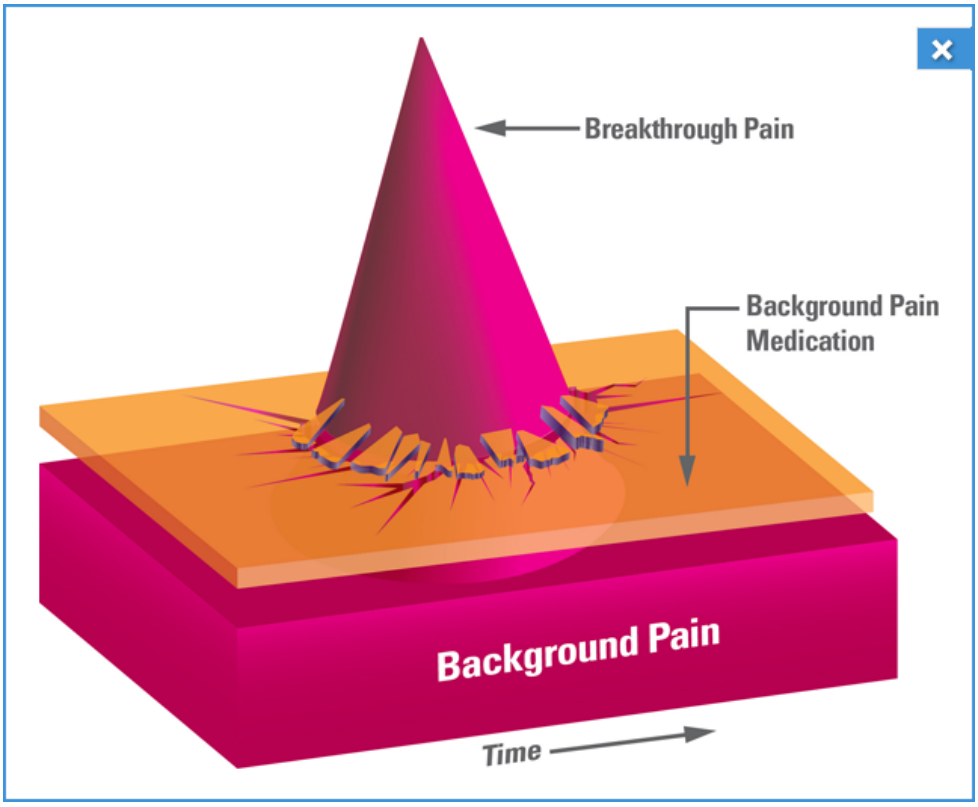
Note: FENTORA is contraindicated in all postoperative pain, including postoperative cancer pain if the patient is not already opioid tolerant. The addition of the qualifier "non-cancer" may be confusing as it could be interpreted to mean that FENTORA can be used for postoperative pain after surgery for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

BREAKTHROUGH PAIN – DEFINITION

Breakthrough cancer pain (BTP) represents "a transitory exacerbation of pain that occurs despite relatively stable and adequately controlled baseline or background pain."[2,3] The prevalence of cancer BTP is high occurring in 50 to 90% of all hospitalized cancer patients.[5] The management of BTP in cancer patients is an important health issue: the incidence of cancer and cancer-related pain has increased.[6]

Breakthrough cancer pain is phenomenologically distinct from persistent chronic cancer pain, also called “baseline pain”. Episodes of breakthrough cancer pain may be predictable, but in about four fifths of patients occur unpredictably.[5] The number of episodes of breakthrough cancer pain per day varies widely. Typically patients have one to four episodes per day.[4]



Source: http://www.breakingthroughpain.com

Use of FENTORA should be limited to four episodes of breakthrough pain per day.

DOSING & ADMINISTRATION[1]

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 micrograms (mcg), 200 mcg, 400 mcg, 600 mcg and 800 mcg fentanyl, as fentanyl citrate. Each tablet strength is marked with a unique identifier.

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

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

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their indicated labeling with respect to patient selection, dosing, and proper conditions for use. Before you prescribe FENTORA, you must review the information in each of the following sections:

- Proper Patient Selection
- Recommended Dose and Dosage Adjustments
- General Opioid Use
- Risks of FENTORA Use

Proper Patient Selection

FENTORA 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.

It is important to minimize the number of strengths available to patients at any time to prevent

confusion and possible overdose.

Recommended Dose and Dosage Adjustment

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

Dose Titration

The goal of dose titration is to find the individual patient's effective and tolerable dose. 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.

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

Dose Titration: 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.

If there is a need to titrate to a higher dose, patients 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 more than four breakthrough pain episodes per day, the dose of the continuous opioid used for persistent pain should be re-evaluated.

General Opioid Use

The American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine and the American Pain Society recognize the following definitions and recommend their use.[7]

Addiction
Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical Dependence
Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance
Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Principles of good medical practice should guide the prescribing of opioids: [8]

- Proper evaluation of the patient is essential.
- A thorough treatment plan includes multiple modalities, documentation of informed consent of risks and benefits, conditions of use and a written patient agreement.
- An opioid trial should not be undertaken in the absence of a complete assessment of the pain complaint.
- Consultation with a specialist in pain medicine or with a psychologist may be warranted.
- Review of treatment should occur periodically, including need for continued opioid therapy and indicators of misuse.
- Documentation is essential for supporting the evaluation, the reason for opioid prescribing, the overall pain management treatment plan, any consultations received, and periodic review of the status of the patient.

The following information was abstracted from: *Substance Abuse in Brief Fact Sheet. Pain Management without Psychological Dependence: A Guide for Healthcare Providers* (see References.)

Reducing the Risk of Psychological Dependence on Opioids: [8]
Psychological dependence not only can hinder the effective treatment of pain, but also can lead to increased pain and related health and social effects. The following are recommended to reduce the risk of opioid psychological dependence while providing effective pain management.

- **Obtain relevant patient background information:** Be aware of patients with a history of personal or familial problems with alcohol or drugs, legal problems, or misuse of prescription drugs; they have an increased chance of becoming psychologically dependent on opioids prescribed for pain.
- **Use screening instruments to identify patients who are at risk or may be opioid dependent:** Use the Opioid Risk Tool, the Pain Medication Questionnaire, the Screener and Opioid Assessment for Patients with Pain, and the Screening Tool for Addiction Risk to identify patients in pain who are at risk for addiction. (See source reference for relevant citations.)
- **Document appropriately:** Have patients sign an agreement outlining the risks and benefits of the proposed treatment plan and other relevant objectives (see source reference for further guidance).
- **Monitor patients closely for symptoms of physical and psychological dependence:** Continually evaluate whether pain is being managed effectively and treatment goals are being met
- Patients taking opioids appropriately for pain management and those whose pain is inadequately relieved may occasionally display inappropriate behaviors, as listed in the cited reference (see above). The possibility of psychological dependence should be considered when a *pattern* of inappropriate behaviors is observed.

Risks of FENTORA Use

Overdose[1]

There is a high risk of overdose if FENTORA is given to:

- Someone for whom it has not been prescribed; or
- Opioid non-tolerant patients.

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 effect being hypoventilation.

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, ventilatory and circulatory status.

To treat overdose (accidental ingestion) in an 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.

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 hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

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 the administration of an opioid antagonist, and as a final alternative, by administration of a neuromuscular blocking agent.

Abuse and Addiction

There is a risk of abuse and addiction from exposure to FENTORA. Fentanyl is a Schedule 1 controlled drug that can produce drug dependence of the morphine type. FENTORA may be subject to misuse, abuse and addiction.

Manage the handling of FENTORA to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since FENTORA may be abused for nonmedical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

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

MORE INFORMATION

For more information about general opioid use, visit the following websites:

- Definitions Related to the Use of Opioids for the Treatment of Pain: Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine

  (http://www.asam.org/docs/publicy-policy-statements/1opioid-definitions-consensus-2-011.pdf?sfvrsn=0)

- Addiction: Substance Abuse & Dependency

  (http://www.cpsa.ab.ca/Resources/PHMC_Overview/PHMC_Addiction_Substance_Abuse_Dependency.aspx)

- Substance Abuse in Brief Fact Sheet. Pain Management Without Psychological Dependence: A Guide for Healthcare Providers

  (http://store.samhsa.gov/shin/content//MS993/MS993.pdf)

Medical Information & Reporting Instructions

For healthcare professionals with specific questions about FENTORA, please contact us at:

MedInfo
Medical Affairs
Teva Canada Innovation
1080 Beaver Hall Hill, Suite 1200
Montreal (Quebec) H2Z 1S8
Call toll-free at 1-855-513-8382
Email: TCIMedical.Affairs@tevapharm.com

Pharmacovigilance Department

You can report any suspected adverse reactions associated with the use of FENTORA either to Teva Canada Limited at 1-800-268-4127 ext. 5005 (English), 1-877-777-9117 (French), Telefax: 1-416-335-4472 or to the Canada Vigilance Program by one of the following 3 ways:

- Report online at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and Fax toll-free to 1-866-678-6789, or Mail to:

  Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario K1A 0K9

IMPORTANT SAFETY INFORMATION

Indications and clinical use:

- Patients considered opioid-tolerant are those who are taking 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.
- Safety and efficacy in pediatric populations (<18 years of age) has not been established.
- Patients over 65 years of age tended to titrate to slightly lower doses than younger patients. Exercise caution when titrating dosage in adults >65 years of age.
- Use of FENTORA is contraindicated in pregnant women.

Contraindications:

- Opioid non-tolerant patient
- Post-operative and acute pain
- Patients with severe respiratory depression or severe obstructive lung conditions
- Patients with known or suspected mechanical gastrointestinal obstruction or any diseases/conditions that affect bowel transit
- 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).

Most serious warnings and precautions:

- **Proper patient selection**: FENTORA 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. Only for use in opioid-tolerant adults of 18 years or older with cancer on continuous opioid therapy for their persistent baseline cancer pain. Contraindicated in patients on intermittent opioids, partial opioid agonists or agents with opioid effects.

- **Fatal respiratory depression**: Fatal respiratory depression has occurred in patients treated with FENTORA, including after use in opioid non-tolerant patients and with improper dosing. Substitution for any other fentanyl product may result in fatal overdose. Due to the risk of respiratory depression, in opioid non-tolerant patients, FENTORA is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Patients must wait at least 4 hours between doses to avoid overdose. Use with CYP P450 3A4 inhibitors may cause fatal respiratory depression.

- **Medication errors:** Do not convert patients on a mcg-per-mcg basis from any other transmucosal fentanyl product to FENTORA. Substitution may result in fatal overdose. If patients are using other opioid-containing products for breakthrough pain, they must be

started on FENTORA at an initial dose of 100 mcg. Regardless of the opioid dose used for baseline cancer pain, patients beginning treatment with FENTORA must begin with titration from the 100 mcg starting dose.

- **Keep out of reach**: Keep FENTORA out of children's sight and reach; accidental ingestion is fatal. FENTORA may be fatal if accidentally ingested by opioid non-tolerant patients.

- **Abuse potential**: Like other Schedule 1 opioid agonists, FENTORA has a high potential for abuse and risk of fatal overdose due to respiratory depression. When prescribing or dispensing FENTORA, consider the potential for misuse, abuse or diversion.

- **Interaction with CNS depressants**: Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death

Other relevant warnings and precautions:

- Intravenous fentanyl may produce bradycardia. Use FENTORA with caution in patients with bradyarrhythmias.
- Concomitant use with CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, benzodiazepines, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages, may produce increased depressant effects, such as respiratory depression, hypotension, and profound sedation.
- Serotonin Syndrome: FENTORA could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. FENTORA should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome.
- Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform, e.g., erythromycin, ketoconazole, and certain protease inhibitors, may increase fentanyl levels, resulting in increased depressant effects.
- Drug dependence/tolerance and withdrawal. Withdrawal may occur in patients who abruptly discontinue treatment or be precipitated by administration of opioid antagonists or mixed agonist/antagonist analgesics.
- Head injury or increased intracranial pressure
- Kidney or liver dysfunction and biliary tract disease, including acute pancreatitis
- Concomitant use with MAO inhibitors
- Psychomotor impairment of mental and/or physical abilities required for dangerous tasks, e.g., driving or operating machinery

- Chronic obstructive pulmonary disease or pre-existing medical conditions that predispose patients to respiratory depression
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility
- 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
- Pregnancy or nursing women. 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. (Fentanyl passes into breast milk and may cause sedation and/or respiratory depression in the breast-fed infant.)
- Do not use FENTORA during labour and delivery
- 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.
- Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids.

For more information:

Please consult the product monograph at http://www.tevacanadainnovation.com/downloads/Fentora_PM_EN.pdf for important information about adverse reactions, drug interactions, and dosing and titration information, which are not discussed here.

The FENTORA product monograph is also available by calling Teva Canada Innovation at 1 855 513-8382.

REFERENCES

1. FENTORA Product Monograph. Teva Canada Innovation, October 07, 2016.
2. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999; 81:129-134.
3. Davies AN, Dickman A, Reid C, *et al*. The management of cancer-related breakthrough pain: Recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain* 2009; 13:331-338.
4. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990; 41:273-281.
5. Margarit C, Julia J, Lopez R, *et al*. Breakthrough cancer pain – Still a challenge. *J Pain Res*. 2012; 5:559-566.
6. Nersesyan H, Slavin KV. Current approach to cancer pain management: Availability and implications of different treatment options *Ther Clin Risk Manag* 2007; 3(3):381–400.
7. Definitions Related to the Use of Opioids for the Treatment of Pain: Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Adoption date: 01-Apr-1997; Rev: 01-Feb-2001. http://www.asam.org/advocacy/find-a-policy-statement/view-policy-statement/public-policy-statements/2011/12/15/definitions-related-to-the-use-of-opioids-for-the-treatment-of-pain-consensus-statement
8. US Department of Health and Human Services. Substance Abuse in Brief Fact Sheet. Pain Management without Psychological Dependence: A Guide for Healthcare Providers. Summer 2006, Volume 4, Issue 1. Available at: http://store.samhsa.gov/shin/content//MS993/MS993.pdf. Accessed 15-NOV-2016.