

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ABSTRAL® (fentanyl) sublingual tablets CII  
Initial U.S. Approval: 1968

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

See full prescribing information for complete boxed warning.

- Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. ABSTRAL is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4, 5.1)
- Accidental ingestion of ABSTRAL, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (2.6, 5.2)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl (5.3, 7)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation (5.4).
- When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ABSTRAL. (2.2, 5.5)
- When dispensing, do not substitute with any other fentanyl products. (5.5)
- ABSTRAL exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.6)
- ABSTRAL is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.7)
- Prolonged use of ABSTRAL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)

### RECENT MAJOR CHANGES

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

### INDICATIONS AND USAGE

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

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

### Limitations of Use (1)

- Not for use in opioid non-tolerant patients.

- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency department. (4)
- As a part of the TIRF REMS Access program, ABSTRAL may be dispensed only to outpatients enrolled in the program. For inpatient administration of ABSTRAL (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

### DOSAGE AND ADMINISTRATION

- Patients must require and use around-the-clock opioids when taking ABSTRAL. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Administer on the floor of the mouth directly under the tongue and allow to completely dissolve. (2.4)
- Initial dose of ABSTRAL: 100 mcg. (2.2)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Individually titrate to a tolerable dose that provides adequate analgesia. (2.3)
- Wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL. (2.3)
- Limit consumption to treat four or fewer breakthrough pain episodes per day once a successful dose is found. (2.3)
- When opioid therapy is no longer required, consider discontinuing ABSTRAL along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.5)

### DOSAGE FORMS AND STRENGTHS

- Sublingual tablets: 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base. (3)

### CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraines dental pain, or use in the emergency department. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of ABSTRAL. (4)

### WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)  
Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue ABSTRAL if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ABSTRAL in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ABSTRAL in patients with impaired consciousness or coma. (5.13)

### ADVERSE REACTIONS

- Most common (total frequency  $\geq 3\%$ ): nausea, somnolence, headache, and constipation. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Sentyln at 1-888-227-8725 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

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

### USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not Recommended. (8.2)
- Renal and Hepatic Impairment: Administer ABSTRAL with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised December 2016

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\* Sections or subsections omitted from the full prescribing information are not listed

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## FULL PRESCRIBING INFORMATION

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

### Life-Threatening Respiratory Depression

Serious, life-threatening and/or fatal respiratory depression has occurred in patients treated with ABSTRAL, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of ABSTRAL or following a dose increase. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose. [see *Warnings and Precautions (5.1)*].

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

### Accidental Ingestion

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

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. ABSTRAL must be kept out of reach of children. [see *Warnings and Precautions (5.2)*; *Patient Counseling Information (17)* and *Storage and Handling (16)*]

### Cytochrome P450 3A4 Interaction

The concomitant use of ABSTRAL with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving ABSTRAL and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.3)*, *Drug Interactions (7)*, *Clinical Pharmacology (12)*].

### Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

- Reserve concomitant prescribing of ABSTRAL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required
- Follow patients for signs and symptoms of respiratory depression and sedation

### Risk of Medication Errors

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

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ABSTRAL.
- When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products.

### Addiction, Abuse, and Misuse

ABSTRAL exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ABSTRAL, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.6)*].

### **Risk Evaluation and Mitigation Strategy (REMS) Access Program**

Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. [see *Warnings and Precautions (5.7)*] Further information is available at [www.TIRFREMSAccess.com](http://www.TIRFREMSAccess.com) or by calling 1-866-822-1483.

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of ABSTRAL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.8)*].

## **1 INDICATIONS AND USAGE**

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

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

### **Limitations of Use:**

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency department [see *Contraindications (4)*].
- As a part of the TIRF REMS Access program, ABSTRAL may be dispensed only to outpatients enrolled in the program [see *Warnings and Precautions (5.7)*]. For inpatient administration of ABSTRAL (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosage and Administration Information**

- Healthcare professionals who prescribe ABSTRAL on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of ABSTRAL [see *Warnings and Precautions (5.7)*].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.6)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating

therapy and following dosage increases with ABSTRAL and adjust the dosage accordingly [see *Warnings and Precautions (5.1)*].

- Instruct patients and caregivers to take steps to store ABSTRAL securely and to properly dispose of unused ABSTRAL as soon as no longer needed [see *Warnings and Precautions (5.2, 5.6)*, *Patient Counseling Information (17)*].
- ABSTRAL is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) [see *Warnings and Precautions (5.5)*].
- ABSTRAL is NOT a generic version of any other oral transmucosal fentanyl product.

## 2.2 Initial Dosage

Initiate treatment with ABSTRAL for all patients with a single initial dose of 100 mcg. The initial dose of ABSTRAL is always 100 mcg, with the only exception being patients already using Actiq.

- If adequate analgesia is obtained within 30 minutes of administration of the 100 mcg tablet, continue to treat subsequent episodes of breakthrough pain with this dose.
- If adequate analgesia is not obtained after ABSTRAL, the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain. [see *Titration and Maintenance of Therapy (2.3)*]
- Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

Due to differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl containing products to ABSTRAL must start with the 100 mcg dose except patients switching from ACTIQ.

ABSTRAL is not equivalent on a mcg per mcg basis with all other fentanyl products, therefore, do not switch patients on a mcg per mcg basis from any other fentanyl product. ABSTRAL is NOT a generic version of any other fentanyl product.

### Conversion of ABSTRAL from Actiq

- a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patients on Actiq. See Table 1 for initial dosing recommendations. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

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

Current ACTIQ Dose (mcg)	Initial ABSTRAL Dose (mcg)
200	100
400	200
600	200
800	200
1200	200
1600	400

- b. For patients converting from Actiq doses of 200 mcg and 400 mcg, initiate titration with 100 mcg and 200 mcg of ABSTRAL, respectively and proceed using multiples of this strength.
- c. For patients converting from Actiq doses of 600 and 800 mcg, initiate titration with 200 mcg and 200 mcg ABSTRAL, respectively and proceed using multiples of this strength.
- d. For patients converting from Actiq doses of 1200 and 1600 mcg, initiate titration with 200 mcg and 400 mcg ABSTRAL, respectively and proceed using multiples of this strength.

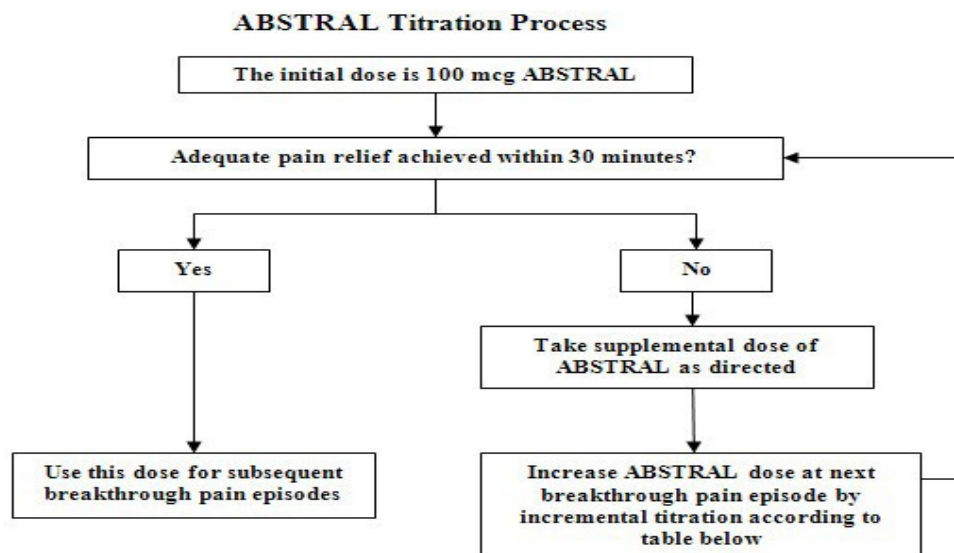
## 2.3 Titration and Maintenance of Therapy

### Titration

The objective of dose titration is to identify an effective and tolerable maintenance dose. From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia using a single ABSTRAL dosage unit per breakthrough cancer pain episode. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased. Patients should record their use of ABSTRAL over several episodes of breakthrough cancer pain and review their experience with their healthcare providers to determine if a dosage adjustment is warranted for management of breakthrough cancer pain episodes. The effective and tolerable dose of Abstral will be determined by dose titration in individual patients.

If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Increase the dose by 100 mcg multiples up to 400 mcg as needed. If adequate analgesia is not obtained with a 400 mcg dose, the next titration step is 600 mcg. If adequate analgesia is not obtained with a 600 mcg dose, the next titration step is 800 mcg. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time. If adequate analgesia is not obtained 30 minutes after the use of ABSTRAL, the patient may repeat the same dose of ABSTRAL. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain. Rescue medication as directed by the health care provider can be used if adequate analgesia is not achieved after use of ABSTRAL.

The efficacy and safety of doses higher than 800 mcg have not been evaluated in clinical studies in patients.



*ABSTRAL dosing for a subsequent episode should be separated by at least 2 hours*

ABSTRAL dose	Using
200 mcg	2 x 100 mcg tablets, <i>or</i> 1 x 200 mcg tablets
300 mcg	3 x 100 mcg tablets, <i>or</i> 1 x 300 mcg tablets
400 mcg	4 x 100 mcg tablets, <i>or</i> 2 x 200 mcg tablets, <i>or</i> 1 x 400 mcg tablets
600 mcg	3 x 200 mcg tablets, <i>or</i> 1 x 600 mcg tablets
800 mcg	4 x 200 mcg tablets, <i>or</i> 1 x 800 mcg tablets

In order to minimize the risk of ABSTRAL-related adverse reactions and to identify the appropriate dose, it is imperative that patients be supervised closely by health professionals during the titration process.

#### Maintenance Therapy

Once titrated to an effective dose, instruct patients to use only one ABSTRAL tablet of the appropriate strength per dose. Maintain patients on this dose.

If adequate analgesia is not obtained after use of ABSTRAL, the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.

Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

#### Dose Re-Adjustment

If the response (analgesia or adverse reactions) to the titrated ABSTRAL dose markedly changes, an adjustment of dose may be necessary to ensure that an appropriate dose is maintained. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the ABSTRAL dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of breakthrough pain and opioid-related adverse reactions.

If more than four episodes of breakthrough pain are experienced per day, re-evaluate the dose of the long-acting opioid used for persistent underlying cancer pain. If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the ABSTRAL dose as necessary to ensure the patient is on an appropriate dose.

Limit the use of ABSTRAL to treat four or fewer episodes of breakthrough pain per day. It is imperative that any dose re-titration is monitored carefully by a healthcare professional.

### **2.4 Administration of ABSTRAL**

Instruct patients to place ABSTRAL tablets on the floor of the mouth directly under the tongue immediately after removal from the blister unit and not to chew, suck, or swallow ABSTRAL tablets. Allow ABSTRAL tablets to completely dissolve in the sublingual cavity. Advise patients not to eat or drink anything until the tablet is completely dissolved.

In patients who have a dry mouth, water may be used to moisten the buccal mucosa before taking ABSTRAL.

### **2.5 Discontinuation of ABSTRAL**

For patients no longer requiring opioid therapy, consider discontinuing ABSTRAL along with a gradual downward titration of other opioids to minimize possible withdrawal effects.

In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, ABSTRAL therapy can usually be discontinued immediately.

### **2.6 Disposal of ABSTRAL**

Patients and their household members must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed. Instructions are included in Patient Counseling Information (17) and in the Medication Guide.

To dispose of any unused ABSTRAL tablets, remove them from the blister cards and flush down the toilet. Do not dispose of the ABSTRAL blister cards or cartons down the toilet.

If additional assistance is required, call 1-888-227-8725.

### 3 DOSAGE FORMS AND STRENGTHS

Sublingual tablets: All tablets are white and available in six strengths, distinguishable by the shape of the tablet and by de- bossing on the tablet surface:

100 microgram tablet: round tablet marked with the number "1"

200 microgram tablet: oval-shaped tablet marked with the number "2"

300 microgram tablet: triangle-shaped tablet marked with the number "3"

400 microgram tablet: diamond-shaped tablet marked with the number "4"

600 microgram tablet: "D"-shaped tablet marked with the number "6"

800 microgram tablet: capsule-shaped tablet marked with the number "8" [*see How Supplied/Storage and Handling (16)*].

### 4 CONTRAINDICATIONS

ABSTRAL is contraindicated in:

- Opioid non-tolerant patients: Life threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients [*see Indications and Usage (1); Warnings and Precautions (5.1)*].
- Acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency department.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.9)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.14)*]
- Known hypersensitivity to fentanyl (e.g., anaphylaxis) [*see Adverse Reactions (6.2)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ABSTRAL, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ABSTRAL.

To reduce the risk of respiratory depression, proper dosing and titration of ABSTRAL are essential [*see Dosage and Administration (2.3)*]. Overestimating the ABSTRAL dosage can result in a fatal overdose with the first dose. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose. [*see Warnings and Precautions (5.5)*].

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

Accidental ingestion of even one dose of ABSTRAL, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

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

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

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

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

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

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

Concomitant use of ABSTRAL with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see *Warnings and Precautions (5.1)*], particularly when an inhibitor is added after a stable dose of ABSTRAL is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in ABSTRAL treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using ABSTRAL with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ABSTRAL-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ABSTRAL until stable drug effects are achieved [see *Dosage and Administration (2.3)*, *Drug Interactions (7)*].

Concomitant use of ABSTRAL with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using ABSTRAL with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see *Dosage and Administration (2.3)*, *Drug Interactions (7)*].

## 5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

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

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

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant,

prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. 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 ABSTRAL is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7) and Patient Counseling Information (17)*].

### 5.5 Risk of Medication Errors

When prescribing, DO NOT convert a patient to ABSTRAL from any other fentanyl products on a mcg per mcg basis from other fentanyl products as ABSTRAL and other fentanyl products are not equivalent on a microgram per microgram basis.

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

There are no safe conversion directions available for patients on any other fentanyl products except ACTIQ [see Dosage and Administration (2.1)]. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of ABSTRAL should always be 100 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [*see Dosage and Administration (2.3)*].

### 5.6 Addiction, Abuse, and Misuse

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

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

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ABSTRAL, and monitor all patients receiving ABSTRAL for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ABSTRAL, but use in such patients necessitates intensive counseling about the risks and proper use of ABSTRAL along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ABSTRAL. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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

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

Required components of the TIRF REMS Access program are:

- Healthcare professionals who prescribe ABSTRAL must review the prescriber educational materials for the TIRF REMS Access program, enroll in the program, and comply with the REMS requirements.
- To receive ABSTRAL, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense ABSTRAL must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute ABSTRAL must enroll in the program and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at [www.TIRFREMSAccess.com](http://www.TIRFREMSAccess.com) or by calling 1-866-822-1483.

## 5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ABSTRAL during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)*].

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

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

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

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

Monitor such patients closely, particularly when initiating and titrating ABSTRAL and when ABSTRAL is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.1)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

### **5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs**

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of ABSTRAL with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see *Drug Interactions (7)*]. This may occur within the recommended dosage range.

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

### **5.11 Adrenal Insufficiency**

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

### **5.12 Severe Hypotension**

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

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

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ABSTRAL may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ABSTRAL.

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

### **5.14 Risk of Use in Patients with Gastrointestinal Conditions**

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

### 5.15 Increased Risk of Seizures in Patients with Seizure Disorders

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

### 5.16 Risks of Driving and Operating Machinery

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

### 5.17 Cardiac Disease

Intravenous administration of fentanyl may produce bradycardia. Therefore, use ABSTRAL with caution in patients with bradyarrhythmias.

## 6 ADVERSE REACTIONS

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

- Life-Threatening Respiratory Depression [*see Warnings and Precautions (5.1)*]
- Interactions with Benzodiazepines and Other CNS Depressants [*see Warnings and Precautions (5.4)*]
- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.6)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.8)*]
- Serotonin Syndrome [*see Warnings and Precautions 5.10*]
- Adrenal Insufficiency [*see Warnings and Precautions (5.11)*]
- Severe Hypotension [*see Warnings and Precautions (5.12)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.14)*]
- Seizures [*see Warnings and Precautions (5.15)*]

### 6.1 Clinical Trials Experience

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

The safety of ABSTRAL has been evaluated in 311 opioid-tolerant cancer patients with breakthrough pain. Two hundred and seventy (270) of these patients were treated in multiple-dose studies. The duration of therapy for patients in multiple-dose studies ranged from 1-405 days with an average duration of 131 days and with 44 patients treated for at least 12 months.

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

The adverse reaction data presented in Table 2 reflect the actual percentage of patients experiencing reactions among patients who received ABSTRAL for breakthrough pain along with concomitant opioid use for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of ABSTRAL therapy or cancer-related symptoms.

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

**Table 2: Adverse Reactions Which Occurred During Titration at a Frequency of  $\geq 5\%$**

System Organ Class Preferred term N (%)	100 mcg (n=22)	200 mcg (n=23)	300 mcg (n=55)	400 mcg (n=38)	600 mcg (n=52)	800 mcg (n=80)	Total (n=270)
<b>Gastrointestinal disorders</b>							
Nausea	1 (4.5)	4 (17.4)	5 (9.1)	1 (2.6)	2 (3.8)	2 (2.5)	15 (5.6)
<b>Nervous system disorders</b>							
Somnolence	0	2 (8.7)	4 (7.3)	2 (5.3)	2 (3.8)	2 (2.5)	12 (4.4)
Dizziness	0	0	3 (5.5)	2 (5.3)	0	1 (1.3)	6 (2.2)
Headache	0	0	0	1 (2.6)	3 (5.8)	1 (1.3)	5 (1.9)

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

**Table 3: Adverse Reactions Which Occurred During Maintenance Therapy at a Frequency of  $\geq 5\%$**

System Organ Class Preferred term, N (%)	100 mcg (n=7)	200 mcg (n=12)	300 mcg (n=22)	400 mcg (n=20)	600 mcg (n=35)	800 mcg (n=72)	Total (n=168)
<b>Gastrointestinal disorders</b>							
Nausea	1 (14.3)	0	2 (9.1)	0	1 (2.9)	6 (8.3)	10 (6.0)
Stomatitis	0	1 (8.3)	1 (4.5)	0	0	1 (1.4)	3 (1.8)
Constipation	0	0	1 (4.5)	2 (10.0)	1 (2.9)	4 (5.6)	8 (4.8)
Dry mouth	0	0	0	1 (5.0)	2 (5.7)	0	3 (1.8)
<b>Nervous system disorders</b>							
Headache	0	0	0	2 (10.0)	1 (2.9)	2 (2.8)	5 (3.0)
Dysgeusia	1 (14.3)	0	0	0	0	1 (1.4)	2 (1.2)
<b>General disorders and administration site conditions</b>							
Fatigue	0	0	0	1 (5.0)	2 (5.7)	0	3 (1.8)
<b>Injury, poisoning and procedural complications</b>							
Accidental overdose	1 (14.3)	0	0	0	0	0	1 (0.6)
<b>Respiratory, thoracic and mediastinal disorders</b>							
Dyspnoea	0	1 (8.3)	0	0	0	0	1 (0.6)
<b>Skin and subcutaneous disorders</b>							
Hyperhidrosis	1 (14.3)	0	0	0	0	1 (1.4)	2 (1.2)

The frequencies listed below represent adverse reactions that occurred in  $\geq 1\%$  of patients from two clinical trials who experienced that reaction while receiving ABSTRAL. Reactions are classified by system organ class.

**Adverse Reactions ( $\geq 1\%$ )**

Cardiac disorders: bradycardia, tachycardia.

Eye disorders: vision blurred.

Gastrointestinal disorders: abdominal pain, abdominal pain upper, aphthous stomatitis, constipation, dry mouth, dyspepsia, gingival ulceration, impaired gastric emptying, lip ulceration, mouth ulceration, nausea, stomach discomfort, stomatitis, tongue disorder, vomiting.

General disorders and administration site conditions: asthenia, drug withdrawal syndrome, fatigue, malaise.

Immune system disorders: drug hypersensitivity.

Injury, poisoning and procedural complications: accidental overdose.

Metabolism and nutrition disorders: anorexia, decreased appetite.

Nervous system disorders: amnesia, disturbance in attention, dizziness, dysgeusia, headache, hypoesthesia, lethargy, parosmia, somnolence, tremor.

Psychiatric disorders: affect lability, anxiety, confusional state, depression, disorientation, dysphoria, euphoric mood, insomnia, mental status changes, paranoia, sleep disorder.

Reproductive system and breast disorders: erectile dysfunction.

Respiratory, thoracic and mediastinal disorder: dyspnea, oropharyngeal pain, throat tightness.

Skin and subcutaneous disorders: hyperhidrosis, night sweats, pruritus, rash, skin lesion.

Vascular disorders: hypotension.

## 6.2 Postmarketing Experience

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

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

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ABSTRAL.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids.

## 7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with ABSTRAL.

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

<b>Inhibitors of CYP3A4</b>	
<i>Clinical Impact:</i>	<p>The concomitant use of ABSTRAL and CYP3A4 inhibitors can increase the plasma concentration of fentanyl resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of ABSTRAL is achieved [see <i>Warnings and Precautions (5.3)</i>].</p> <p>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.</p>
<i>Intervention:</i>	<p>If concomitant use is necessary, consider dosage reduction of ABSTRAL until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, consider increasing the ABSTRAL dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
<i>Examples:</i>	<p>Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir) grapefruit juice.</p>

<b>CYP3A4 Inducers</b>	
<i>Clinical Impact:</i>	The concomitant use of ABSTRAL with CYP3A4 inducers can decrease the plasma concentrations of fentanyl [see <i>Clinical Pharmacology (12.3)</i> ], resulting in decreased efficacy or onset of withdrawal syndrome in patients who have developed physical dependence to fentanyl [see <i>Warnings and Precautions (5.6)</i> ]  After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i> ], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the ABSTRAL dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ABSTRAL dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	rifampin, carbamazepine, phenytoin
<b>Benzodiazepines and other Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation, [see <i>Warnings and Precautions (5.4)</i> ].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
<b>Serotonergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see <i>Warnings and Precautions 5.10</i> ].
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ABSTRAL if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.10)</i> ] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.1)</i> ].
<i>Intervention:</i>	The use of ABSTRAL is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranylcypromine, linezolid
<b>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</b>	
<i>Clinical Impact:</i>	May reduce the analgesic effect of ABSTRAL and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine

<b>Muscle Relaxants</b>	
<i>Clinical Impact:</i>	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ABSTRAL and/or the muscle relaxant as necessary.
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when ABSTRAL is used concomitantly with anticholinergic drugs.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy - Category C

There are no adequate and well-controlled studies in pregnant women.

#### Risk Summary:

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with ABSTRAL in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### *Fetal/Neonatal Adverse Reactions*

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

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

##### *Labor or Delivery*

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. ABSTRAL is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid

analgesics, including ABSTRAL, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

## Data

### *Human Data*

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

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

### *Animal Data*

Fentanyl has been shown to be embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of ABSTRAL on a mg/m<sup>2</sup> basis) and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of ABSTRAL based on a mg/m<sup>2</sup> basis). There was no evidence of teratogenicity reported.

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

## **8.2 Lactation**

### Risk Summary

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

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

### Clinical Considerations

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

## **8.3 Females and Males of Reproductive Potential**

### Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.1), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

The safety and efficacy of ABSTRAL have not been established in patients below 18 years of age.

## **8.5 Geriatric Use**

Of the 270 opioid tolerant patients with breakthrough cancer pain in the Phase 3 clinical studies of ABSTRAL, 58 (21%) were 65 years of age and older. There was no difference in the median titrated dose in patients aged 65 years and older compared to those <65 years. No clinically meaningful difference was noted in the safety profile of the group 65 years of age and older as compared to younger patients in

ABSTRAL clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger adult population. Therefore, exercise caution when individually titrating ABSTRAL in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ABSTRAL slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.9)*].

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

## **8.6 Patients with Renal and Hepatic Impairment**

Insufficient information exists to make recommendations regarding the use of ABSTRAL in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and the inactive metabolite is mostly eliminated in urine. If the drug is used in these patients, use the drug with caution because of the reduced hepatic metabolism and renal excretion capacity in such patients.

## **8.7 Sex**

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

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

ABSTRAL contains fentanyl, a Schedule II substance.

## **9.2 Abuse and Addiction**

ABSTRAL contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. ABSTRAL can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.6)*].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers

and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

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

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

#### Risks Specific to Abuse of ABSTRAL

ABSTRAL is for oral transmucosal use only. Abuse of ABSTRAL poses a risk of overdose and death. The risk is increased with concurrent abuse of ABSTRAL with alcohol and other central nervous system depressants.

### **9.3 Dependence**

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

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

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

## **10 OVERDOSAGE**

#### Clinical Presentation

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

#### Treatment of Overdosage

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

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in ABSTRAL, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as

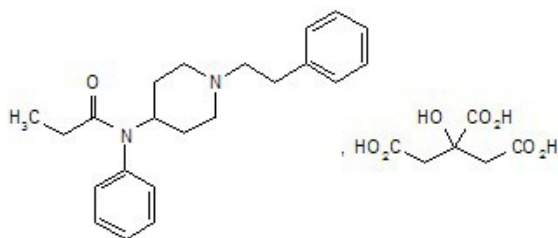
directed by the product's prescribing information.

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

## 11 DESCRIPTION

ABSTRAL (fentanyl) sublingual tablet is a solid formulation of fentanyl citrate, an opioid agonist, intended for oral sublingual administration. ABSTRAL is formulated as a white tablet available in six strengths (100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg), distinguishable by the shape of the tablet and by de-bossing on the tablet surface.

**Active Ingredient:** Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



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

**Inactive Ingredients:** Croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

#### Effects on the Central Nervous System

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

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

#### Effects on the Gastrointestinal Tract and Other Smooth Muscle

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food 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.

#### Effects on the Cardiovascular System

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

#### Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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

#### Effects on the Immune System

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

#### Concentration–Efficacy Relationships

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

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. [*see Dosage and Administration (2.3)*].

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [*see Dosage and Administration (2.2, 2.3)*].

#### Concentration–Adverse Reaction Relationships

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

#### Respiratory System

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

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may cause rigidity in the muscles of respiration resulting in respiratory difficulties [*see Warnings and Precautions (5.1)*].

### **12.3 Pharmacokinetics**

#### Absorption

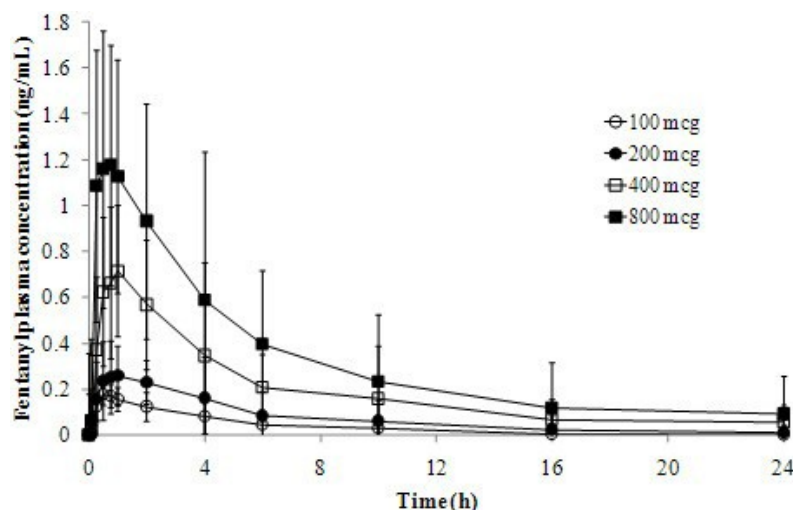
Fentanyl is a highly lipophilic drug. Orally administered fentanyl undergoes pronounced hepatic and

intestinal first pass effects. Absorption of fentanyl from ABSTRAL sublingual tablets is mainly through the oral mucosa.

The bioavailability of ABSTRAL sublingual tablets has been calculated to be 54%.

Dose proportionality across the 100 mcg to 800 mcg ABSTRAL dose range has been demonstrated (Table 4). Mean plasma fentanyl levels following single doses of ABSTRAL are shown in Figure 1. The median time to maximum plasma concentration (T<sub>max</sub>) across these four doses of ABSTRAL varied from 30 to 60 minutes (range of 15 - 240 minutes).

**Figure 1: Mean (+/- SD) Plasma Fentanyl Concentration versus Time after Administration of Single Doses of 100 mcg, 200 mcg, 400 mcg and 800 mcg ABSTRAL to Healthy Subjects**



Pharmacokinetic parameters are presented in Table 5.

**Table 5. Mean (CV%) Fentanyl Pharmacokinetic Parameters after Single-Dose Administration of 100, 200, 400 and 800 mcg Doses of ABSTRAL to Healthy Subjects (n=12 per Dose Level)**

Parameter	Unit	Abstral dose			
		100 mcg	200 mcg	400 mcg	800 mcg
C <sub>max</sub>	(ng/mL)	0.187 (33)	0.302 (31)	0.765 (38)	1.42 (33)
T <sub>max</sub>	(min)	30 [19-120]	52 [16-240]	60 [30-120]	30 [15-60]
AUC <sub>0-inf</sub>	(ng.h/mL)	0.974 (34)	1.92 (27)	5.49 (35)	8.95 (33)
T <sub>1/2</sub>	(h)	5.02 (51)	6.67 (30)	13.5 (37)	10.1 (34)

a: median (range)

In another study, dose proportionality between 800 mcg and 1600 mcg in C<sub>max</sub> and AUC has also been demonstrated.

Pharmacokinetic studies have shown that multiple tablets are bioequivalent to single tablets of the equivalent dose.

### Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. 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 free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V<sub>ss</sub>) was 4 L/kg.

### Elimination

#### *Metabolism*

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies [see *Drug Interactions (7)*].

#### *Excretion*

Fentanyl is more than 90% eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the 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 was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg).

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of fentanyl have not been performed.

#### Mutagenesis

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

#### Impairment of Fertility

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

## **14 CLINICAL STUDIES**

The efficacy of ABSTRAL was investigated in a clinical trial in opioid tolerant adult patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in patients with cancer experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for 1 week or longer. All patients were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain.

A double-blind, placebo-controlled, crossover study was performed in patients with cancer to evaluate the effectiveness of ABSTRAL for the treatment of breakthrough cancer pain. Open-label titration identified a dose of ABSTRAL in which a patient obtained adequate analgesia with tolerable side effects, within the range of 100 mcg to 800 mcg. In the double-blind efficacy study, patients who identified a successful dose were randomized to a sequence of 10 treatments; seven with ABSTRAL and three with placebo.

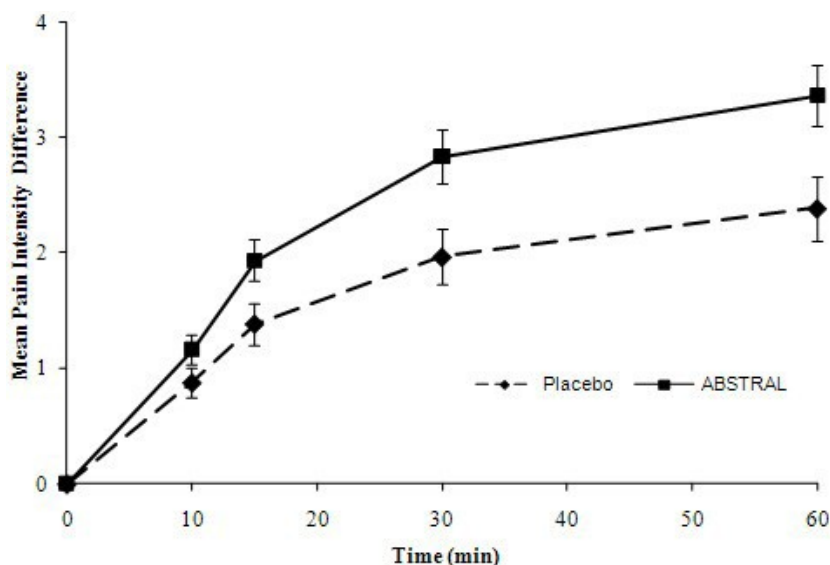
Of the 131 patients who entered the titration phase of the study, 78 (60%) achieved a successful dose during the titration phase. Sixty-six patients entered the double-blind phase and 60 completed the study. The dose of ABSTRAL was determined by titration starting at 100 mcg. The final titrated dose of ABSTRAL for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain. In a second open-label safety study using an identical titration regimen, 96 of 139 patients (69%) who entered the study titrated to a dose in which the patient obtained adequate analgesia with tolerable side effects during the titration phase. Table 5 presents the final titrated dose for both the double-blind efficacy and open-label safety studies.

**Table 6: Final dose of ABSTRAL following initial titration in all clinical efficacy and safety studies**

ABSTRAL Dose	N=174 n (%)
100 mcg	11 (6)
200 mcg	15 (9)
300 mcg	35 (20)
400 mcg	25 (14)
600 mcg	40 (23)
800 mcg	48 (28)

The primary outcome measure, the mean sum of pain intensity difference at 30 minutes (SPID30) for ABSTRAL-treated episodes was statistically significantly higher than for placebo-treated episodes.

**Figure 2: Mean Pain Intensity Difference ( $\pm$ SE) for ABSTRAL Compared to Placebo**



## 16 HOW SUPPLIED/STORAGE AND HANDLING

ABSTRAL is supplied in six dosage strengths. Tablets are supplied in child-resistant, protective blister cards with peelable foil. Each blister card contains 4 tablets, in pack sizes of 32 (all strengths) tablets. Each tablet is white in color, with the strength distinguishable by the shape of the dosage unit and by de-bossing on the tablet surface:

Dosage Strength (fentanyl base)	Tablet Shape	Tablet Markings	Carton/Blister Package Color	Pack size	NDC Number
100 mcg	Round	"1"	Light blue	32	42358-100-32
200 mcg	Oval	"2"	Dark orange	32	42358-200-32
300 mcg	Triangle	"3"	Brown	32	42358-300-32
400 mcg	Diamond	"4"	Violet	32	42358-400-32
600 mcg	"D"	"6"	Turquoise	32	42358-600-32
800 mcg	Capsule	"8"	Indigo	32	42358-800-32

Note: Colors and shapes are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

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

### Life-Threatening Respiratory Depression

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

### Increased Risk of Overdose and Death in Children Due to Accidental Ingestion

- Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure [see *Warnings and Precautions (5.2)*].
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*].
- Instruct patients to take steps to store ABSTRAL securely and to dispose of unused ABSTRAL by removing them from the blister cards and flushing down the toilet [see *Disposal of Unopened ABSTRAL Blister Packages When No Longer Needed*].
- Instruct patients and caregivers to keep both used and unused ABSTRAL out of the reach of children [see *Warnings and Precautions (5.2)*]

### Interactions with Benzodiazepines and Other CNS Depressants

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

### Addiction, Abuse, and Misuse

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

### Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Advise patients of the following information pertaining to the TIRF REMS

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

### Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and

to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. [see *Warnings and Precautions (5.10), Drug Interactions (7)*].

#### MAOI Interaction

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

#### Adrenal Insufficiency

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

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

- Instruct patients not to take ABSTRAL for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Inform patients on the meaning of opioid tolerance and that ABSTRAL is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.
- Advise patients that, if they are not taking an opioid medication on a regular around-the-clock basis, they must not take ABSTRAL.
- Instruct patients to place ABSTRAL tablets on the floor of the mouth directly under the tongue immediately after removal from the blister unit.
- Instruct patients not to chew, suck, or swallow ABSTRAL tablets.
- Instruct patients to allow ABSTRAL tablets to completely dissolve in the sublingual cavity.
- Advise patients not to eat or drink anything until the tablet is completely dissolved [see *Dosage and Administration (2.4), ABSTRAL Medication Guide*].
- In patients who have a dry mouth, water may be used to moisten the buccal mucosa before taking ABSTRAL. Instruct patients not to take more than 2 doses of ABSTRAL for each episode of breakthrough cancer pain.
- Instruct patients to wait two hours before treating a new episode of breakthrough pain with ABSTRAL.
- Instruct patients NOT to share ABSTRAL and that sharing ABSTRAL with anyone else could result in the other individual's death due to overdose.
- Instruct patients to use ABSTRAL exactly as prescribed by their doctor and not to take ABSTRAL more often than prescribed.

#### Hypotension

Inform patients that ABSTRAL may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions (5.12)*].

### Anaphylaxis

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

### Pregnancy

#### *Neonatal Opioid Withdrawal Syndrome*

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

#### *Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that ABSTRAL can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

### Lactation

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

### Infertility

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

### Driving or Operating Heavy Machinery

Inform patients that ABSTRAL may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.16)*].

### Constipation

Advise patients of the potential for severe cons and when to seek medical attention [*see Adverse Reactions (6)*].

### Disposal of Unused ABSTRAL

- Advise patients and their household members to dispose of any unopened packs remaining from a prescription as soon as they are no longer needed.
- Instruct patients that, to dispose of any unused ABSTRAL tablets, remove them from the blister cards and flush them down the toilet. Do not dispose of the ABSTRAL blister cards or cartons down the toilet.
- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of ABSTRAL are provided in the ABSTRAL Medication Guide. Ensure patients read this information in its entirety and give them an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess units that remain in the home after the drug is no longer needed, instruct them to call the toll-free number for Sentyln Therapeutics, Inc. 1-888-227-8725 or seek assistance from their local DEA office.

Manufactured by:

Pharmaceuticals International, Inc.  
Hunt Valley, MD 21031

Manufactured for and Distributed by:

Sentyln Therapeutics, Inc.  
Solana Beach, CA 92075

**Medication Guide**  
**ABSTRAL® (AB-stral) CII**  
**(fentanyl)**  
**Sublingual tablets**

**IMPORTANT:**

Do not use ABSTRAL unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant).

You can ask your healthcare provider if you are opioid tolerant.

Keep ABSTRAL in a safe place away from children.

Get emergency medical help right away if:

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

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

**ABSTRAL is:**

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

**Important information about ABSTRAL:**

- **Get emergency help right away if you take too much ABSTRAL (overdose).** When you first start taking ABSTRAL, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking ABSTRAL with other opioid medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, **confusion**, breathing problems, coma, and death.
- Never give anyone else your ABSTRAL. They could die from taking it. Store ABSTRAL away from children and in a safe place to prevent stealing or abuse. Selling or giving away ABSTRAL is against the law.
- If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using ABSTRAL. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
- ABSTRAL is available only through a program called the **Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access program**. To receive ABSTRAL, you must:
  - talk to your healthcare provider
  - understand the benefits and risks of ABSTRAL
  - agree to all of the instructions
  - sign the Patient-Prescriber Agreement form

- ABSTRAL is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your ABSTRAL prescription filled.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

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

**Do not take ABSTRAL if:**

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

**Before taking ABSTRAL, tell your healthcare provider if you have a history of:**

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

**Tell your healthcare provider if you are:**

- **pregnant or planning to become pregnant.** Prolonged use of ABSTRAL during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** ABSTRAL passes into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking ABSTRAL with certain other medicines can cause serious side effects that could lead to death

### When taking ABSTRAL:

- Do not change your dose. Take ABSTRAL exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Instructions for Use at the end of this Medication Guide for information about how to use ABSTRAL.**
- **Use ABSTRAL tablets whole.**
- **Do not crush, split, suck, or chew ABSTRAL tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using ABSTRAL. If there is any of the ABSTRAL tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- You must not use more than 2 doses of ABSTRAL for each episode of breakthrough cancer pain.
- Use **1** dose of ABSTRAL for an episode of breakthrough cancer pain.
- If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of ABSTRAL, you can use **only 1** more dose of ABSTRAL as instructed by your healthcare provider.
- If your breakthrough pain does not get better after the second dose of ABSTRAL, call your healthcare provider for instructions. **Do not use another dose of ABSTRAL at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with ABSTRAL.
- If you only need to take 1 dose of ABSTRAL for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of ABSTRAL for a **new** episode of breakthrough pain.
- If you need to use 2 doses of ABSTRAL for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of ABSTRAL for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using ABSTRAL.
- Talk to your healthcare provider if your dose of ABSTRAL does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of ABSTRAL needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.
- Do not stop taking ABSTRAL without talking to your healthcare provider.
- After you stop taking, or when ABSTRAL is no longer needed, see “**How should I dispose of unused ABSTRAL tablets when they are no longer needed?**” for proper disposal of ABSTRAL.
- **DO NOT** Drive or operate heavy machinery, until you know how ABSTRAL affects you. ABSTRAL can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ABSTRAL may cause you to overdose and die.
- **DO NOT Switch from ABSTRAL to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of ABSTRAL is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of ABSTRAL that may be different than other fentanyl containing medicines you may have been taking.

### How should I store ABSTRAL?

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

### How should I dispose of unopened ABSTRAL tablets when they are no longer needed?

- Dispose of any unopened ABSTRAL units remaining from a prescription as soon as you no longer need them:

- remove the tablets from the blister cards and flush them down the toilet.
- Do not flush the ABSTRAL blister cards, units or cartons down the toilet.
- If you need help with disposal of ABSTRAL, call 1-888-227-8725 or call your local Drug Enforcement Agency (DEA) office.

### General information about ABSTRAL

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

This Medication Guide summarizes the most important information about ABSTRAL. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about ABSTRAL that is written for healthcare professionals. For more information about the TIRF REMS Access program, go to [www.TIRFREMSAccess.com](http://www.TIRFREMSAccess.com) or call 1- 866-822-1483.

### What are the ingredients in ABSTRAL?

Active Ingredient: fentanyl citrate

Inactive Ingredients: croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose.

### Patient Instructions for Use

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

### When you get an episode of breakthrough pain, take the dose prescribed by your healthcare provider as follows:

- If your mouth is dry, take a sip of water to moisten it. Spit out or swallow the water. Dry your hands if they are wet before you handle ABSTRAL tablets.
- ABSTRAL comes in a blister card with 4 blister units. Each blister unit contains an ABSTRAL tablet. It is important that the tablet stays sealed in the blister unit until you are ready to use it.
- When you are ready to take an ABSTRAL tablet, pull apart 1 of the blister units from the blister card by tearing along the dotted lines (perforations) until it is fully separated. (See Figures 1 and 2)



Figure 1

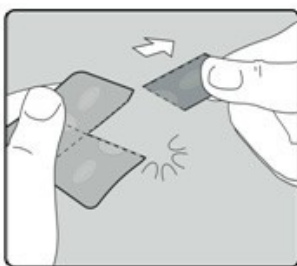


Figure 2

- When the blister unit is fully separated, peel back the foil starting at the unsealed area where indicated. Gently remove the tablet. **Do not** try to push ABSTRAL tablets through the foil. This will damage the tablet. (See Figures 3 and 4)

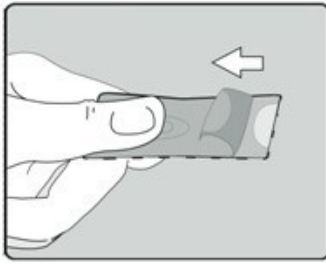


Figure 3

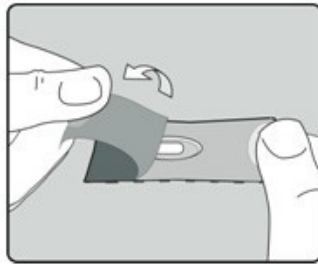


Figure 4

- As soon as you remove the ABSTRAL tablet from the blister unit:
  - place it on the floor of your mouth, under your tongue, as far back as you can (See Figures 5, 6, and 7).



Figure 5



Figure 6



Figure 7

- If more than 1 tablet is required, spread them around the floor of your mouth under your tongue.
- Let the tablet dissolve completely.  
ABSTRAL dissolves under your tongue and will be absorbed by your body to help provide relief for your breakthrough cancer pain.
- **Do not suck, chew or swallow the tablet.**
- You should not drink or eat anything until the tablet has completely dissolved under your tongue and you can no longer feel it in your mouth.

Manufactured by:  
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Manufactured for:  
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