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: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL
See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, ABSTRAL is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)**
- **Keep out of reach of children. (5.3)**
- **Use with CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ABSTRAL. (2.1, 5.2)**
- **When dispensing, do not substitute with any other fentanyl products. (5.2)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **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. (5.10)**

RECENT MAJOR CHANGES

Dosage and Administration, Conversion from Actiq (2.2)	11/2014

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 opioid therapy for their underlying persistent cancer pain. (1)
Limitations of Use:
ABSTRAL may be dispensed only to patients enrolled in the TIRF REMS Access program.

DOSAGE AND ADMINISTRATION

- Patients must require and use around-the-clock opioids when taking ABSTRAL (1)
- Initial dose of ABSTRAL: 100 mcg. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.1)
- Wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL. (2.1)
- Limit consumption to treat four or fewer breakthrough pain episodes per day once a successful dose is found. (2.4)
- Administer on the floor of the mouth directly under the tongue and allow to completely dissolve. (2. 5)

DOSAGE FORMS AND STRENGTHS

- Sublingual tablet in 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg strengths. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraines dental pain. (4)
- Intolerance or hypersensitivity to fentanyl or components of ABSTRAL. (4)

WARNINGS AND PRECAUTIONS

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1, 5.4)
- Do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. (5.2)
- ABSTRAL contains fentanyl in a dose that can be fatal to a child. Ensure proper storage and disposal. (5.3, 16.3)
- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4, 7)
- Titrate ABSTRAL cautiously in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation, and in patients susceptible to intracranial effects of CO_2 retention. (5.6, 5.7)

ADVERSE REACTIONS

- Most common (total frequency ≥ 3%): nausea, somnolence, headache, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 1-888-227-8725 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- See Boxed Warning and Warnings and Precautions (5)

USE IN SPECIFIC POPULATIONS

- Administer ABSTRAL with caution to patients with renal or hepatic dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide.

Revised: November 2014

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

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

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)]*

ABSTRAL must be kept out of reach of children. *[see Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of ABSTRAL with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression. *[see Drug Interactions (7)]*

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 that could result in fatal overdose.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ABSTRAL. *(2.1)***
- **When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products.**

ABUSE POTENTIAL

ABSTRAL contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. ABSTRAL can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

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 **E**valuation **and M**itigation **S**trategy **(REMS).** Under the TIRF (**T**ransmucosal **I**mmediate **R**elease **F**entanyl) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program [see *Warnings and Precautions* (5.10)]. Further information is available at www.TIRFREMSAccess.com or by calling1-866-822-1483.

1 INDICATIONS AND USAGE

ABSTRAL (fentanyl) sublingual tablets are 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 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 daily, or at least 25 mcg of transdermal fentanyl/hour, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or at least 25 mg oral oxymorphone daily, 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.

ABSTRAL is contraindicated for patients who are not already tolerant to opioids because life-threatening respiratory depression and death could result at any dose in patients not on a chronic regimen of opioids. For this reason, ABSTRAL is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

ABSTRAL is intended to be prescribed only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Limitations of Use:

As a part of the TIRF REMS Access program, ABSTRAL may be dispensed only to outpatients enrolled in the

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

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* (5.10)].

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

2.1 Dose Titration

The objective of dose titration is to identify an effective and tolerable maintenance dose for ongoing management of breakthrough cancer pain episodes. The effective and tolerable dose of ABSTRAL will be determined by dose titration in individual patients.

Carefully supervise patients until a dose that provides adequate analgesia with tolerable side effects is reached for breakthrough pain control.

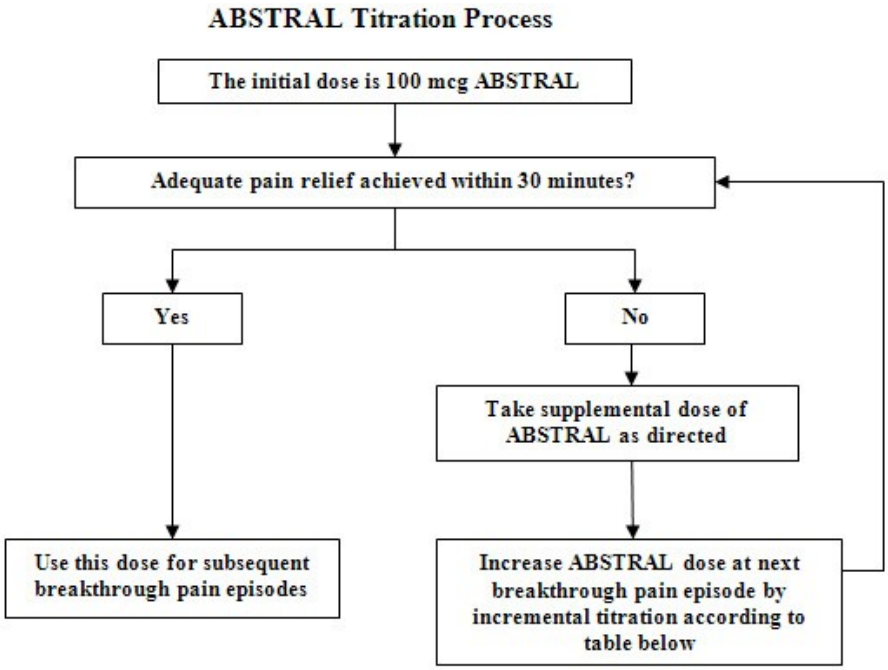
Starting Dose: Individually titrate ABSTRAL to a dose that provides adequate analgesia with tolerable side effects. Begin titration of **all** patients with an initial dose of ABSTRAL of 100 mcg. Due to differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl containing products to ABSTRAL must start with the 100 mcg dose. However, for patients converting from Actiq, see Table 1: Initial Dosing Recommendations for Patients on 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.

Start all patients with a single 100 mcg tablet.

- 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 health care 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.

Titration Steps: 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, *or* 1 x 200 mcg tablets
300 mcg	3 x 100 mcg tablets, *or* 1 x 300 mcg tablets
400 mcg	4 x 100 mcg tablets, *or* 2 x 200 mcg tablets, *or* 1 x 400 mcg tablets
600 mcg	3 x 200 mcg tablets, *or* 1 x 600 mcg tablets
800 mcg	4 x 200 mcg tablets, *or* 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.

2.2 Conversion from Actiq

The initial dose of Abstral is always 100 mcg with the only exception being patients already using 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 mcg
400	200 mcg
600	200 mcg
800	200 mcg
1200	200 mcg
1600	400 mcg

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 Maintenance Therapy

Once an appropriate dose for pain management has been established, 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 health care 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.

2.4 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 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.

2.5 Administration of ABSTRAL

Place ABSTRAL tablets on the floor of the mouth directly under the tongue immediately after removal from the blister unit. Do not 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.

2.6 Discontinuation of Therapy

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.

3 DOSAGE FORMS AND STRENGTHS

ABSTRAL is formulated as a sublingual tablet and is available in six strengths, distinguishable by the shape of the tablet and by de- bossing on the tablet surface. All tablets are white:

100 microgram tablet is a round tablet marked with the number "1"

200 microgram tablet is an oval-shaped tablet marked with the number "2"
300 microgram tablet is a triangle-shaped tablet marked with the number "3"
400 microgram tablet is a diamond-shaped tablet marked with the number "4"
600 microgram tablet is a "D"-shaped tablet marked with the number "6"
800 microgram tablet is a capsule-shaped tablet marked with the number "8"

[see *How Supplied/Storage and Handling* (16.4)].

4 CONTRAINDICATIONS

ABSTRAL is contraindicated in the management of pain in opioid non-tolerant patients, because life-threatening hypoventilation could occur at any dose in patients not already taking around-the-clock opioid therapy. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, or at least 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

ABSTRAL is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

ABSTRAL is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

5 WARNINGS AND PRECAUTIONS

See *Boxed Warning* - WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

5.1 Hypoventilation (Respiratory Depression)

Serious or fatal respiratory depression can occur even at recommended doses in patients using ABSTRAL. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses, including ABSTRAL, in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid- induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 ABSTRAL and Other Fentanyl Products

ABSTRAL is NOT equivalent to all other fentanyl products used to treat breakthrough pain on a mcg per mcg basis. There are differences in the pharmacokinetics of ABSTRAL relative to other fentanyl products which could potentially result in clinically important differences in the amount of fentanyl absorbed and could result in a fatal overdose.

When prescribing ABSTRAL to a patient, DO NOT convert on a mcg to mcg basis from other fentanyl products. Directions for safely converting patients to ABSTRAL from other fentanyl products are not currently available except for Actiq [see *Conversion from Actiq* (2.2)]. This includes oral, transdermal, or parenteral formulations of fentanyl. Therefore, for opioid-tolerant patients starting treatment for breakthrough pain, the initial dose of ABSTRAL is 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects. [See *Dosage and Administration* (2.1)]

When dispensing ABSTRAL to a patient, DO NOT substitute it for any other fentanyl product prescription.

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal to a child. Even though ABSTRAL is provided in child-resistant packaging, patients and their caregivers must be instructed to keep tablets out of the reach of children. [see *How Supplied/Storage and Handling* (16.1, 16.2), and *Patient Counseling Information* (17.1, 17.2)].

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

Physicians 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.

5.4 Additive CNS Depressant Effects

The concomitant use of ABSTRAL with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [see *Drug Interactions* (7)].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects and the dose of ABSTRAL adjusted, if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking ABSTRAL of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause hypoventilation, titrate ABSTRAL with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of ABSTRAL may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer ABSTRAL with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury; use only if clinically warranted.

5.8 Cardiac Disease

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

5.9 MAO Inhibitors

ABSTRAL is not recommended for use in patients who have received MAO inhibitors within the past 14 days. Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

5.10 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 or by calling 1-866-822-1483.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse event 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 most commonly observed adverse reactions with ABSTRAL include typical opioid adverse reactions, such as nausea, constipation, somnolence and headache. Expect opioid side effects and manage them accordingly.

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.

Table2: Adverse Reactions Which Occurred During Titration at a Frequency of ≥ 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)

Gastrointestinal disorders							
Nausea	1 (4.5)	4 (17.4)	5 (9.1)	1 (2.6)	2 (3.8)	2 (2.5)	15 (5.6)
Nervous system disorders							
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 ≥ 5% within the total population that occurred after a successful dose had been determined.

Table3: Adverse Reactions Which Occurred During Maintenance Therapy at a Frequency of ≥ 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)**
Gastrointestinal disorders							
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)
Nervous system disorders							
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)
General disorders and administration site conditions							
Fatigue	0	0	0	1 (5.0)	2 (5.7)	0	3 (1.8)
Injury, poisoning and procedural complications							
Accidental overdose	1 (14.3)	0	0	0	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders							
Dyspnoea	0	1 (8.3)	0	0	0	0	1 (0.6)
Skin and subcutaneous disorders							
Hyperhidrosis	1 (14.3)	0	0	0	0	1 (1.4)	2 (1.2)

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

Adverse Reactions (≥ 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.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when ABSTRAL is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of ABSTRAL with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving ABSTRAL who begin therapy with, or increase the dose of, CYP3A4 inhibitors need to be carefully monitored for signs of opioid toxicity over an extended period of time. Increase dosage conservatively.

The concomitant use of ABSTRAL with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of ABSTRAL.

Patients receiving ABSTRAL who stop therapy with, or decrease the dose of, CYP3A4 inducers need to be monitored for signs of increased ABSTRAL activity and the dose of ABSTRAL must be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy - Category C

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

Use ABSTRAL during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

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.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg intravenously or 160 mcg/kg subcutaneously. Conversion to human equivalent doses indicates this is within

the range of the human recommended dosing for ABSTRAL.

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

8.2 Labor and Delivery

Fentanyl readily crosses the placenta. Therefore do not use ABSTRAL during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use ABSTRAL in women who are nursing because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ABSTRAL.

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.

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 Gender

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender 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. Schedule II opioid substances such as fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have a high potential for abuse and addiction. ABSTRAL is also subject to misuse and criminal diversion.

9.2 Abuse and Addiction

Manage the handling of ABSTRAL to minimize the risk of misuse, including the restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [see *How Supplied/Storage and Handling* (16.2, 16.3)].

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

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

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

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

Contact your State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Physical dependence is not ordinarily a concern in the treatment of patients with chronic cancer pain, and fear of tolerance and physical dependence must not deter using opiate doses that adequately relieve the pain. Guide the administration of Abstral by the response of the patient.

Opioid analgesics may cause physical dependence that can result in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of ABSTRAL overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation [see *Clinical Pharmacology* (12.2)].

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the ABSTRAL tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and administer naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated

administration may be necessary. Consult the package insert of the individual opioid antagonist for details.

10.4 Treatment of Overdosage in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but at the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of severe ABSTRAL overdose includes: securing a patent airway, assisting or controlling ventilation and establishing intravenous access. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

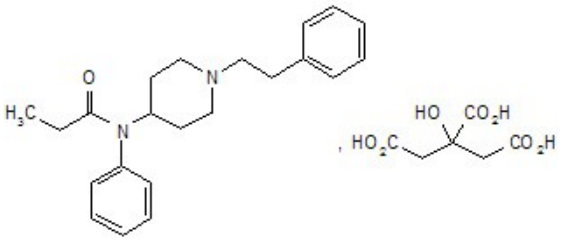
Carefully observe and appropriately manage patients with overdose until their clinical condition is well controlled.

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

11 DESCRIPTION

ABSTRAL (fentanyl) sublingual tablet is a solid formulation of fentanyl citrate, a potent opioid analgesic intended for oral sublingual administration. ABSTRAL is formulated as a white tablet available in six strengths, 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 a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics,

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

Analgesia

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, individually titrate the dose of ABSTRAL to achieve the desired effect [see *Dosage and Administration* (2)].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a μ-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

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

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid induced-effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin secretion, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species (e.g., rats and dogs). Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

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 these 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. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may cause rigidity in the muscles of respiration resulting in respiratory difficulties. Therefore, be aware of this potential complication [see *Boxed Warning - Warnings: Importance Of Proper Patient Selection and Potential for Abuse, Contraindications* (4),

Warnings And Precautions (5.1), *Adverse Reactions* (6), and *Overdosage* (10)].

12.3 Pharmacokinetics

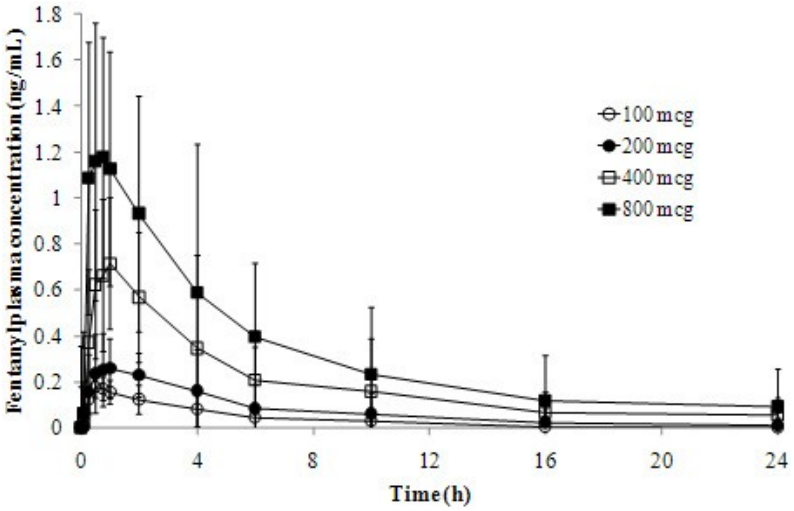
Absorption

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 (Table4). Mean plasma fentanyl levels following single doses of ABSTRAL are shown in Figure 1. The median time to maximum plasma concentration (T_{max}) 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 4.

Table 4. 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_{max}	(ng/mL)	0.187 (33)	0.302 (31)	0.765 (38)	1.42 (33)
T_{max}[a]	(min)	30 [19-120]	52 [16-240]	60 [30-120]	30 [15-60]
$AUC_{0\text{-}inf}$	(ng.h/mL)	0.974 (34)	1.92 (27)	5.49 (35)	8.95 (33)
$T_{1/2}$	(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_{max} 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 (Vss) was 4 L/kg.

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)].

Elimination

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

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

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.

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.

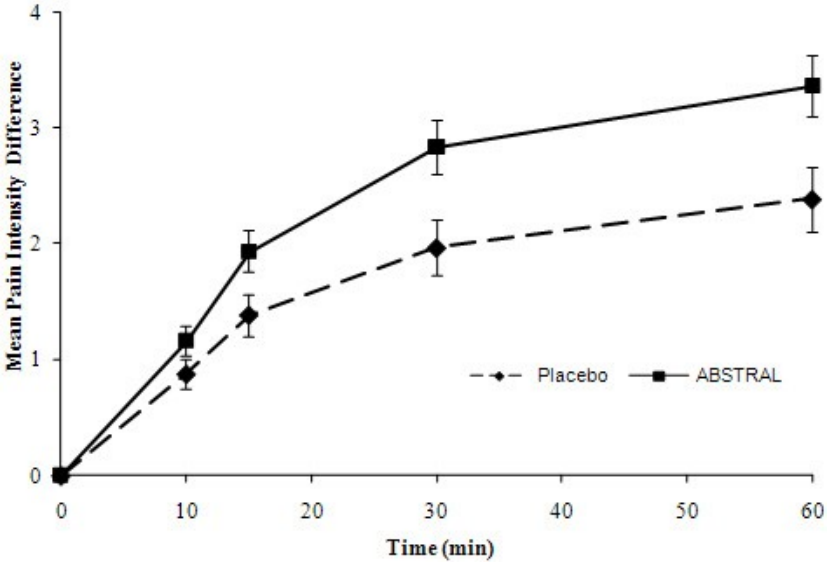
Of the 131 patients who entered the titration phase of the study, 78 (60%) achieved a successful dose during the titration phase. Sixty- six patients entered the double-blind phase and 60 completed the study. The dose of ABSTRAL was determined by titration starting at 100 mcg. The final titrated dose 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 5: 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 (±SE) for ABSTRAL Compared to Placebo



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

ABSTRAL is supplied in individually sealed child-resistant blister packages contained in a cardboard outer carton, in pack sizes of 12 (100 mcg, 200 mcg, 300 mcg and 400 mcg strengths) or 32 (all strengths) tablets. The packaging is color-coded for each ABSTRAL tablet strength.

The amount of fentanyl contained in ABSTRAL can be fatal to a child, individual for whom it is not prescribed or non-opioid tolerant adult. Patients and their caregivers must be instructed to keep ABSTRAL out of the reach of children [see *Boxed Warning - Warnings: Potential For Abuse and Importance Of Proper Patient Selection* and *Warnings And Precautions* (5), and *Patient Counseling Information* (17.1)].

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.

16.2 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* (17.2) 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 Sentynl Therapeutics, Inc. at 1-888-227-8725.

16.3 How Supplied

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 12 (100 mcg, 200 mcg, 300 mcg and 400 mcg strengths) or 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	12 32	57881-331-12 57881-331-32
200 mcg	Oval	"2"	Dark orange	12 32	57881-332-12 57881-332-32
300 mcg	Triangle	"3"	Brown	12 32	57881-333-12 57881-333-32
400 mcg	Diamond	"4"	Violet	12 32	57881-334-12 57881-334-32
600 mcg	"D"	"6"	Turquoise	32	57881-336-32
800 mcg	Capsule	"8"	Indigo	32	57881-338-32

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient/Caregiver Instructions

- Before initiating treatment with Abstral, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time Abstral is dispensed because new information may be available.
- TIRF REMS Access Program
  - Outpatients 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 a component of the TIRF REMS Access program, prescribers must 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 outpatient that only enrolled health care providers may prescribe Abstral.
  - Patient 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.
- Instruct patients and their caregivers that ABSTRAL contains medicine in an amount that could be fatal in children, in individuals for whom ABSTRAL is not prescribed, and in those who are not opioid tolerant.

Patients and their caregivers must be instructed to keep ABSTRAL, both used and unused dosage units, out of the reach of children. Patients and their caregivers must be instructed to dispose of any unneeded tablets remaining from a prescription as soon as possible [see How Supplied/Storage and Handling (16.2), and Warnings and Precautions (5.2).]

- Instruct patients and their caregivers to read the Medication Guide each time ABSTRAL is dispensed because new information may be available.
- 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.
- Instruct patients on the meaning of opioid tolerance and Abstral is only to be used as a supplemental pain medication for patients with pain requiring regular opioids, who have developed tolerance to the opioid medication and who need additional opioid treatment of breakthrough pain episodes.
- Instruct that if they are not taking an opioid medication on a regular around-the-clock basis, they must not take Abstral.
- You must not take more than 2 doses of ABSTRAL for each episode of breakthrough cancer pain.
- You must 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.
- Advise patients that Abstral contains fentanyl, which is a pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Advise patients that the active ingredient in Abstral, fentanyl, is a drug that some people abuse. Abstral is to be taken only by the patient for whom it was prescribed, and protected from theft or misuse in the work or home environments.
- Instruct patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking Abstral.
- Instruct patients to use Abstral exactly as prescribed by their doctor and not to take Abstral more often than prescribed.
- Caution patients that Abstral can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking Abstral of these dangers and counsel accordingly.
- Warn patients not to combine Abstral with alcohol, sleep aids, or tranquilizers except by order of the prescribing physician, because dangerous additive effects may occur resulting in serious injury or death.
- Inform female patients that if they become pregnant or plan to become pregnant during treatment with Abstral to ask their doctor about the effects that Abstral (or any medicine) may have on them and their unborn child.

Disposal of Unopened ABSTRAL Blister Packages When No Longer Needed

- 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 1-888-227-8725 or seek assistance from their local DEA office.