ABSTRAL® (fentanyl) sublingual tablets CII from FULL PRESCRIBING INFORMATION

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

Black Box Warning
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 Evaluation and Mitigation Strategy (REMS). Under the TIRF (Transmucosal Immediate Release Fentanyl) 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.

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

<table>
<thead>
<tr>
<th>Current ACTIQ Dose (mcg)</th>
<th>Initial Abstral Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100 mcg</td>
</tr>
<tr>
<td>400</td>
<td>200 mcg</td>
</tr>
<tr>
<td>600</td>
<td>200 mcg</td>
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<tr>
<td>800</td>
<td>200 mcg</td>
</tr>
<tr>
<td>1200</td>
<td>200 mcg</td>
</tr>
<tr>
<td>1600</td>
<td>400 mcg</td>
</tr>
</tbody>
</table>

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.

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.

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 Galena Biopharma, Inc. at 1-888-227-8725.

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