CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022510Orig1s000

REMS

NDA 22-510

ABSTRAL® (fentanyl) sublingual tablets

Opioid Analgesic

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PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each ABSTRAL prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe ABSTRAL for <u>outpatient</u> use are specially certified.

a. ProStrakan will ensure that healthcare providers who prescribe ABSTRAL for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe ABSTRAL, prescribers will be required to enroll in the ABSTRAL REMS program. Prescribers must complete the following requirements to be enrolled:

i. Review the ABSTRAL REMS prescriber educational materials (*Prescriber Education Program*), including the Full Prescribing Information, and successfully complete the knowledge assessment (*Prescriber Knowledge Assessment*).

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I understand the responsible use conditions for ABSTRAL and the risks and benefits of chronic opioid therapy.

b) I understand that ABSTRAL can be abused, and that this risk should be

considered when prescribing or dispensing ABSTRAL in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that ABSTRAL is indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

d) I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that ABSTRAL must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.

f) I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg), and that patients must be titrated individually.

g) I understand that ABSTRAL is not bioequivalent with any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to ABSTRAL must not be converted on a microgram-per-microgram basis.

h) I will complete and sign an ABSTRAL REMS *Patient-Prescriber Agreement* with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.

In signing the *Patient-Prescriber Agreement*, the prescriber documents the following:

1) Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.

2) Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms 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 one week or longer.

3) The ABSTRAL Medication Guide has been provided to and reviewed with the patient or their caregiver

4) The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of ABSTRAL including communication of the following safety messages:

A. If patients stop taking their around-the-clock opioid medication, they must stop taking ABSTRAL.

B. NEVER share ABSTRAL

C. Giving ABSTRAL to someone for whom it has not been prescribed can result in a fatal overdose.

D. ABSTRAL can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

In signing the *Patient-Prescriber Agreement,* the patient and/or their caregiver document the following:

1) My prescriber has given me a copy of the ABSTRAL Medication Guide and has reviewed it with me.

2) I understand that before I can take ABSTRAL, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking ABSTRAL.

4) I understand how I should take ABSTRAL, including how much I can take, and how often I can take it.

5) I understand that ABSTRAL can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take ABSTRAL exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if ABSTRAL does not relieve my pain. I will not change my dose of ABSTRAL myself or take ABSTRAL more often than my prescriber has directed.

7) I agree that I will never give ABSTRAL to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store ABSTRAL in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of unused and remaining ABSTRAL and will dispose of ABSTRAL as soon as I no longer need it.

10) I understand that selling or giving away ABSTRAL is against the law.

11) I have asked my prescriber all the questions I have about ABSTRAL. If I have any additional questions or concerns in the future about my treatment with ABSTRAL, I will contact my prescriber.

12) I have reviewed the Patient Authorization for Disclosure and Use of Health Information for ABSTRAL REMS Statement and I agree to its terms and conditions which authorize my healthcare providers and health plans to disclose my personal and medical information to ProStrakan, Inc., (the maker of ABSTRAL) and their agents and contractors to administer the REMS program.

i) I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the ABSTRAL REMS program (by fax, or through the ABSTRAL REMS website) within ten (10) working days.

j) At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.

k) I understand that ABSTRAL is only available through the ABSTRAL REMS program. I understand and agree to comply with the ABSTRAL REMS program requirements for prescribers.

b. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new *Patient-Prescriber Agreement* at least every two (2) years.

c. ProStrakan will:

i. Ensure that prescriber enrollment can successfully be completed via the ABSTRAL REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, prescribers receive the following materials that are part of the ABSTRAL REMS program and are appended:

- *The ABSTRAL REMS Program Overview(Prescribers)*
- *Prescriber Education Program*
- *Prescriber Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement*
- *ABSTRAL REMS Website*

iii. Ensure that prescribers have successfully completed the knowledge assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the ABSTRAL REMS program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the ABSTRAL REMS program, and therefore, are certified to prescribe ABSTRAL.

v. Monitor education and enrollment requirements for prescribers and may

inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that at least 2 weeks prior to first availability of ABSTRAL to healthcare providers, a *Dear Healthcare Provider Letter* will be sent. The target audience for the letter will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe oral transmucosal fentanyl products. The letter will include information on the risks associated with the use of ABSTRAL and will explain to healthcare providers that if they wish to treat patients using ABSTRAL, they must enroll in the ABSTRAL REMS program. The letter will be accompanied by a copy of the Full Prescribing Information (which will include the Medication Guide), and will be available on the ABSTRAL REMS website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the ABSTRAL REMS Program and is appended.

2. ABSTRAL will only be dispensed by pharmacies that are specially certified.

a. ProStrakan will ensure that ABSTRAL will only be dispensed by certified pharmacies. To become certified to dispense ABSTRAL, each pharmacy must be enrolled in the ABSTRAL REMS program.

b. Each pharmacy will be required to designate an authorized pharmacist to complete enrollment on behalf of the pharmacy.

c. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals, hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to enroll their **outpatient pharmacy:**

i. Review the ABSTRAL REMS education program (*Pharmacy Education Program)* and successfully complete the *Pharmacy Knowledge Assessment*.

ii. Ensure the pharmacy enables their pharmacy management system to support communication with the ABSTRAL REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I understand the risks and benefits associated with ABSTRAL and the requirements of the ABSTRAL REMS program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing ABSTRAL have been educated on the risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program, as described in the *Pharmacy Education Program*. This training should be documented and is subject to audit.

c) I understand that ABSTRAL is not bioequivalent with other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products.

d) I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg).

f) I understand the importance of discussing the risks and benefits of ABSTRAL with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the ABSTRAL Medication Guide must be given to the patient or their caregiver each time ABSTRAL is dispensed.

h) I understand that ABSTRAL will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL ABSTRAL prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the ABSTRAL REMS program to dispense ABSTRAL.

k) I understand that ABSTRAL can only be obtained from wholesalers/distributors that are enrolled in the ABSTRAL REMS program.

l) I understand that our pharmacy will not sell, loan or transfer ABSTRAL inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the ABSTRAL REMS program and successfully complete the enrollment requirements every two (2) years.

n) I understand that ABSTRAL is only available through the REMS program. I understand that the pharmacy must comply with the ABSTRAL REMS program requirements for outpatient pharmacies.

e. ***Inpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the ABSTRAL REMS education program (*Pharmacy Education Program*) and successfully complete the *Pharmacy Knowledge Assessment.*

ii. Complete and sign the *Pharmacy Enrollment Form.* In signing the *Pharmacy Enrollment Form* the authorized pharmacist is required to acknowledge the following:

a) I understand the benefits and risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program, as described in the *Pharmacy Education Program.*

c) I understand that ABSTRAL is not bioequivalent to other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products.

d) I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg).

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the ABSTRAL REMS program to dispense ABSTRAL to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy is not to dispense ABSTRAL for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with an ABSTRAL prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the REMS program, as described in section B.1 of this REMS.

i) I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the ABSTRAL REMS.

j) I understand that our pharmacy will not sell, loan or transfer ABSTRAL inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that ABSTRAL can only be obtained from wholesalers/distributors that are enrolled in the ABSTRAL REMS program.

l) I understand that our pharmacy must re-enroll in the ABSTRAL REMS program every two (2) years.

m) I understand that ABSTRAL is available only through the ABSTRAL REMS program. I understand and agree to comply with the ABSTRAL REMS program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years

g. ProStrakan will:

i. Ensure that pharmacy enrollment can successfully be completed via the ABSTRAL REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, pharmacies receive the following materials that are part of the ABSTRAL REMS program and are appended:

- *The ABSTRAL REMS Program Overview (Outpatient Pharmacy or Inpatient Pharmacy, as applicable)*
- *Pharmacy Education Program*
- *Pharmacy Enrollment Form(Outpatient or Inpatient, as applicable)*
- *Pharmacy Knowledge Assessment*
- *ABSTRAL REMS Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the knowledge assessment before activating a pharmacy's enrollment in the ABSTRAL REMS program. For outpatient pharmacies only, ProStrakan will also ensure that the upgrades to the pharmacy management system have been validated before enrolling a pharmacy in the ABSTRAL REMS program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the ABSTRAL REMS program, and therefore, certified to dispense ABSTRAL.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

vi. Ensure that at least 2 weeks prior to first availability of ABSTRAL to healthcare

providers, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing ABSTRAL. The letter will include information on the risks associated with the use of ABSTRAL and the requirements of the ABSTRAL REMS program. The letter will be accompanied by a copy of the Full Prescribing Information (which will include the Medication Guide), and will be available on the ABSTRAL REMS website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the ABSTRAL REMS Program and are appended.

3. ABSTRAL will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. ProStrakan will ensure that ABSTRAL will only be dispensed for outpatient use if there is documentation in the ABSTRAL REMS system that the dispensing pharmacy, prescriber, and patient are all enrolled and active in the ABSTRAL REMS program.

b. Patients are passively enrolled in the ABSTRAL REMS program when their first ABSTRAL prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the ABSTRAL REMS system. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2.a-d, respectively.

c. Prior to dispensing ABSTRAL, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the ABSTRAL prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient

   ii. If one or more of the required enrollments cannot be verified, the ABSTRAL REMS system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

   i. The patient has not filled a prescription for more than six (6) months

   ii. The patient receives prescriptions for ABSTRAL from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the ABSTRAL REMS program cannot fill the prescription for ABSTRAL until the new prescriber is active in the ABSTRAL REMS program.

f. A patient may have more than one current prescriber (e.g., pain management

specialist, primary care physician) provided that prescriptions for ABSTRAL are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. ProStrakan will ensure that wholesalers/distributors who distribute ABSTRAL are enrolled in the ABSTRAL REMS program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving ABSTRAL inventory for distribution:

   a. Review the distributor ABSTRAL REMS program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the ProStrakan (by fax, scan and e-mail, mail or through the ABSTRAL REMS website). In signing the *Distributor Enrollment Form*, each distributor is required to indicate they understand that ABSTRAL is available only through the ABSTRAL REMS program and that they must comply with program requirements, and acknowledge that:

      i. I will ensure that relevant staff are trained on the ABSTRAL REMS program procedures and will follow the requirements of the ABSTRAL REMS program.

      ii. I will ensure that ABSTRAL is only distributed to pharmacies whose enrollment has been validated in the ABSTRAL REMS program.

      iii. I will provide data to the ABSTRAL REMS program including information on shipment to enrolled pharmacies.

      iv. I will cooperate with periodic audits or non-compliance investigations to ensure that ABSTRAL is distributed in accordance with the program requirements.

   c. ProStrakan will ensure that all forms are complete, prior to enrolling a distributor in the ABSTRAL REMS program.

   d. ProStrakan will notify distributors when they are enrolled in the ABSTRAL REMS program, and therefore, able to distribute ABSTRAL.

   e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

   f. Distributors will be re-educated and re-enrolled in the ABSTRAL REMS program every two (2) years.

   g. The following distributor materials are part of the ABSTRAL REMS program and

are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*

2. ProStrakan will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the ABSTRAL REMS requirements.
3. ProStrakan will develop a REMS system that uses existing pharmacy management systems that allow for the transmission of REMS information using established telecommunication standards. The REMS system should incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the REMS requirements, if deemed necessary in the future.
4. ProStrakan will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing ABSTRAL. Additionally, ProStrakan will monitor to ensure that ABSTRAL is only being dispensed for outpatient use to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by ProStrakan if noncompliance is found.
5. ProStrakan will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement* with each ABSTRAL patient, and to submit it to the REMS program within ten (10) business days. This will be accomplished through patient surveys and by reconciling the *Patient-Prescriber Agreements* submitted to the REMS program with patient enrollment data captured through the pharmacy management system.
6. ProStrakan will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the ABSTRAL REMS program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
7. ProStrakan will evaluate enrolled inpatient pharmacies' compliance with REMS requirements through surveys.
8. ProStrakan will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the ABSTRAL REMS program.
9. ProStrakan will ensure that all materials listed in or appended to the ABSTRAL REMS will be available through the ABSTRAL website www.abstralrems.com or by calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725).
10. ProStrakan will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the REMS program. Notifications for patients will be sent to the patient's prescriber.
11. If there are substantive changes to the ABSTRAL REMS Program, ProStrakan will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the ABSTRAL REMS program are defined as:

a. Significant changes to the operation of the ABSTRAL REMS program.

b. Changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of ABSTRAL.

12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, ProStrakan will take reasonable steps to improve implementation of these elements and to maintain compliance with the ABSTRAL REMS program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

ProStrakan will submit REMS Assessments to the FDA every six (6) months for the first year following the approval of the ABSTRAL REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date of the assessment. ProStrakan will submit each assessment so that it will be received by the FDA on or before the due date.

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ABSTRAL® (fentanyl) sublingual tablets; FDA required restricted distribution program

Dear Healthcare Provider

ProStrakan, Inc. would like to inform you of the approval of ABSTRAL (fentanyl) sublingual tablets. Because of the risk of misuse, abuse, addiction, and overdose, ABSTRAL is only available through the FDA mandated ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program, a restricted distribution program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting.

For inpatient administration of ABSTRAL, patient and prescriber enrollment in the ABSTRAL REMS program is not required.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

In order for you to take part in the ABSTRAL REMS program, and prescribe ABSTRAL in an outpatient setting, you must:

- Review the Prescriber Education Program
- Successfully complete the Prescriber Knowledge Assessment
- Complete the Prescriber Enrollment Form
- Complete and sign a **Patient-Prescriber Agreement** with each new patient
- Re-enroll every two years

To enroll in the ABSTRAL REMS program, visit www.abstralrems.com or call 1-888-ABSTRAL (1-888-227-8725).

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products. Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

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.

Medication Guide

It is important that you discuss the risks of ABSTRAL with your patients and encourage them to read the Medication Guide (see attached copy). The Medication Guide provides important information on the safe and effective use of ABSTRAL and will be provided to patients with each prescription. Patients should be counseled on the need to store ABSTRAL safely out of the reach of children and household acquaintances.

Adverse Event Reporting

Prescribers should report all adverse events associated with the use of ABSTRAL directly to ProStrakan at 1-888-ABSTRAL (1-888-227-8725).

Please see the attached Full Prescribing Information, including boxed warnings, and Medication Guide for important safety information for ABSTRAL.

If you have questions about ABSTRAL or the ABSTRAL REMS program, please visit www.abstralrems.com for more information or call the toll-free number, 1-888-ABSTRAL (1-888-227-8725).

Thank you,

The ABSTRAL REMS Team.

This letter is required and approved by the FDA as part of the ABSTRAL REMS program.

Dear Prescriber

Welcome, and thank you for your interest in ABSTRAL® (fentanyl) sublingual tablets and the ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is available only through the FDA mandated ABSTRAL REMS program, a restricted distribution program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting.

For inpatient administration of ABSTRAL, patient and prescriber enrollment in the ABSTRAL REMS program is not required. Only the inpatient pharmacy is required to be enrolled to order and dispense ABSTRAL. Inpatient pharmacies may not dispense ABSTRAL for outpatient use.

In order for you to take part in the ABSTRAL REMS program, and prescribe ABSTRAL in an outpatient setting, you must:

- Review the Prescriber Education Program
- Successfully complete the Prescriber Knowledge Assessment
- Complete the Prescriber Enrollment Form
- Complete and sign a **Patient-Prescriber Agreement** with each new patient
- Re-enroll every two years

To enroll in the ABSTRAL REMS program, visit www.abstralrems.com or call 1-888-ABSTRAL (1-888-227-8725).

To help you understand the ABSTRAL REMS program, materials are included in this kit, including the ABSTRAL REMS program:

- Prescriber Welcome Letter
- Prescriber Program Overview
- Prescriber Education Program
- Prescriber Knowledge Assessment Form
- Prescriber Enrollment Form

Also included in this kit is a complete set of materials for patients. You can order additional patient kits by calling 1-888-ABSTRAL (1-888-227-8725). Each patient kit includes The ABSTRAL REMS program:

- Patient Welcome Letter
- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Further copies of all ABSTRAL REMS program documents can be obtained from the ABSTRAL REMS website. For any questions or additional information about ABSTRAL or the ABSTRAL REMS program, feel free to contact the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725) or online at www.abstralrems.com.

Thank you,

The ABSTRAL REMS team

This letter is required and approved by the FDA as part of the ABSTRAL REMS program.

ABSTRAL® (fentanyl) sublingual tablets

The ABSTRAL REMS Program Prescriber Enrollment Form

I understand that ABSTRAL (fentanyl) sublingual tablets are only available through the ABSTRAL REMS program and I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the ABSTRAL Full Prescribing Information and the *Prescriber Education Program*, and I have completed the *Prescriber Knowledge Assessment*. I understand the responsible use conditions for ABSTRAL and the risks and benefits of chronic opioid therapy.
2. I understand that ABSTRAL can be abused, and that this risk should be considered when prescribing or dispensing ABSTRAL in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that ABSTRAL is indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
4. I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that ABSTRAL must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.
6. I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg), and that patients must be titrated individually.
7. I understand that ABSTRAL is not bioequivalent with any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to ABSTRAL must not be converted on a microgram-per-microgram basis.
8. I will complete and sign an ABSTRAL REMS *Patient-Prescriber Agreement* with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.
9. I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the ABSTRAL REMS program (by fax or through the ABSTRAL REMS website) within ten (10) working days.
10. At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.
11. I understand that ABSTRAL is only available through the ABSTRAL REMS program. I understand and agree to comply with the ABSTRAL REMS program requirements for prescribers.

Prescriber Signature _____ **Date** _____

First Name _____ **Last Name** _____ **Credentials** _____

Prescriber Information

Site Name* _____

Address _____

City _____ **State** _____ **Zip Code** _____

State License Number* _____ **State Issued** _____

DEA Number* _____ **National Provider Identifier (NPI)** _____

Specialty _____ **Phone** _____

Fax _____ **E-mail** _____

Please fax the completed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424). You will receive enrollment confirmation via email or fax. For questions regarding the ABSTRAL REMS program, call 1-888-ABSTRAL (1-888-227-8725).

* If you have additional sites, state license or DEA numbers that you may use when prescribing ABSTRAL, please complete overleaf.

Additional Prescriber Information

Site Name _____
Address _____
City _____ **State** _____ **Zip Code** _____
Phone _____ **Fax** _____

Site Name _____
Address _____
City _____ **State** _____ **Zip Code** _____
Phone _____ **Fax** _____

Site Name _____
Address _____
City _____ **State** _____ **Zip Code** _____
Phone _____ **Fax** _____

DEA Number _____
DEA Number _____
DEA Number _____

State License Number _____ **State Issued** _____
State License Number _____ **State Issued** _____
State License Number _____ **State Issued** _____

This form is required and approved by the FDA as part of the ABSTRAL REMS.

The ABSTRAL REMS Program - An Overview for Prescribers

This booklet is required and approved by FDA as part of the ABSTRAL REMS.

What is the ABSTRAL REMS Program?

The ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program is designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are on treatment, to ensure appropriate use of ABSTRAL® (fentanyl) sublingual tablets. 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 the ABSTRAL REMS program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting.

For inpatient administration of ABSTRAL, patient and prescriber enrollment in the ABSTRAL REMS program is not required. Only the inpatient pharmacy is required to be enrolled to order and dispense ABSTRAL for inpatient use. Inpatient pharmacies may not dispense ABSTRAL for outpatient use.

In order to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of ABSTRAL, you will be enrolled only after successful completion of the knowledge assessment. Educational opportunities and knowledge assessment questions are available online at the ABSTRAL REMS program website (www.abstralrems.com) or by contacting the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725) to request materials. You will be required to attest to your understanding of the appropriate use of ABSTRAL and adherence to the ABSTRAL REMS program.

Without this enrollment, you will not be eligible to prescribe ABSTRAL for outpatient use. In addition, only enrolled pharmacies are eligible to dispense ABSTRAL prescriptions. Outpatient prescriptions written by unenrolled prescribers, or for unenrolled patients will not be authorized by the ABSTRAL REMS program and will not be dispensed to the patient.

Prescribers and pharmacies are required to acknowledge their understanding of the potential risks involved with the inappropriate use of ABSTRAL. Prescribers and pharmacies should ensure:

- **Completion of the relevant education program and knowledge assessment, and submission of the relevant enrollment forms to the ABSTRAL REMS program.**
- **Appropriate patient selection.**
- **Completion and submission of a patient-prescriber agreement to the ABSTRAL REMS program (not required for inpatients).**
- **That patients are provided with relevant ABSTRAL REMS program materials and educated on the benefits and risks of treatment with ABSTRAL.**

Overview of Steps for the ABSTRAL REMS Program

Step 1 Prescriber Education & Enrollment (Outpatient Use)

- Review the ABSTRAL REMS prescriber educational materials including the Full Prescribing Information, and successfully complete the Prescriber Knowledge Assessment.
- Complete and sign the Prescriber Enrollment Form and re-new the agreement every two (2) years.
- Receive a secure username and password to be able to access the ABSTRAL REMS program at www.abstralrems.com.

Step 2 Patient Education

- Identify appropriate patients.
- Counsel the patient about the benefits and risks of ABSTRAL and together review the Medication Guide.
- Encourage the patient to ask questions.
- Complete the Patient-Prescriber Agreement, which must be signed by both you and your patient (not required for inpatients).
- Submit the signed Patient-Prescriber Agreement to the ABSTRAL REMS program via fax or through the ABSTRAL REMS website at www.abstralrems.com
- This agreement needs to be submitted within 10 business day of completing the agreement. If this form is not received by the ABSTRAL REMS program, the patients' next prescription for ABSTRAL will not be authorized.

Step 3 Prescribing

- Write prescription for ABSTRAL.
- Help each patient to find pharmacies which are certified in the ABSTRAL REMS program. A list of ABSTRAL REMS certified pharmacies can be located on www.abstralrems.com or by calling 1-888-ABSTRAL (1-888-227-8725).

Step 4 Monitoring

- Promptly report suspected adverse events including misuse, abuse, and overdose directly to ProStrakan by calling 1-888-ABSTRAL (1-888-227-8725).
- Respond to requests for additional information from the ABSTRAL REMS program.

For more information you can call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or visit www.abstralrems.com

Important Safety Information

Boxed Warnings

WARNINGS: **POTENTIAL FOR ABUSE AND** ***IMPORTANCE OF PROPER PATIENT SELECTION***

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

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

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products.

Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

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 the ABSTRAL REMS (**R**isk **E**valuation and **M**itigation **S**trategy). Under the ABSTRAL REMS, healthcare professionals who prescribe to outpatients, outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense and distribute ABSTRAL, respectively. Further information is available at www.abstralrems.com or by calling 1-888-227-8725.

Warnings and Precautions

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 from other fentanyl products. Directions for safely converting patients to ABSTRAL from other fentanyl products are not currently available. (Note: 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.

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

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.

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.

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.

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.

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

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.

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.

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.

Cardiac Disease

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

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.

Adverse Reactions

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.

If you have any questions or require additional information or further copies of all ABSTRAL REMS documents, please visit either www.abstralrems.com or www.abstral.com, or call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

www.abstralrems.com
www.abstral.com

ABSTRAL® (fentanyl) sublingual tablets

The ABSTRAL REMS Program Patient-Prescriber Agreement

As the prescriber of ABSTRAL I acknowledge that:

1. Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.
2. Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms 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 one week or longer.
3. The ABSTRAL Medication Guide has been provided to and reviewed with the patient or their caregiver.
4. The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of ABSTRAL including communication of the following safety messages:
   a. If patients stop taking their around-the-clock opioid medication, they must stop taking ABSTRAL.
   b. NEVER share ABSTRAL.
   c. Giving ABSTRAL to someone for whom it has not been prescribed can result in a fatal overdose.
   d. ABSTRAL can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

Prescriber

Signature _____ **First Name** _____ **Last Name** _____

Credentials _____ **DEA Number** _____ **Fax Number** _____ **Date** _____

As the patient being prescribed ABSTRAL, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the ABSTRAL Medication Guide and has reviewed it with me.
2. I understand that before I can take ABSTRAL, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking ABSTRAL.
4. I understand how I should take ABSTRAL, including how much I can take, and how often I can take it.
5. I understand that ABSTRAL can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take ABSTRAL exactly as my prescriber has directed me to take it.
6. I agree to contact my prescriber if ABSTRAL does not relieve my pain. I will not change my dose of ABSTRAL myself or take ABSTRAL more often than my prescriber has directed.
7. I agree that I will never give ABSTRAL to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store ABSTRAL in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of unused and remaining ABSTRAL and will dispose of ABSTRAL as soon as I no longer need it.
10. I understand that selling or giving away ABSTRAL is against the law.
11. I have asked my prescriber all the questions I have about ABSTRAL. If I have any additional questions or concerns in the future about my treatment with ABSTRAL, I will contact my prescriber.
12. I have reviewed the Patient Authorization for Disclosure and Use of Health Information for ABSTRAL REMS Statement and I agree to its terms and conditions which authorize my healthcare providers and health plans to disclose my personal and medical information to ProStrakan, Inc., (the maker of ABSTRAL) and their agents and contractors to administer the REMS program.

Patient
Signature _____ **Date** _____

First Name _____ **Middle Initial** ____ **Last Name** _____ **ZIP** _____

Date of Birth (MM/DD/YYYY) ____ /_____ /_____ **Phone Number** _____

Patient representative (if required)
Signature _____ **Relationship to Patient** _____

Date _____ **First Name** _____ **Last Name** _____

Please fax the completed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424). For questions regarding the ABSTRAL REMS program, call 1-888-ABSTRAL (1-888-227-8725).

Patient Authorization for Disclosure and Use of Health Information for ABSTRAL REMS Program

I hereby authorize each of my physicians, pharmacists, and other healthcare providers (together, my "Providers") and each of my health insurers (together, my "Insurers") to disclose my personally identifiable health information, including information related to my medical diagnosis, condition, and treatment (including lab and prescription information), and my name, address, and telephone number (together, my "Health Information") to ProStrakan, Inc., its agents and representatives, including third parties authorized by ProStrakan, Inc. to administer the ABSTRAL REMS program (together, "ProStrakan") for the purposes described below.

Specifically, I authorize ProStrakan to receive, use, and disclose my Health Information in order to:

I. Enroll me in the ABSTRAL REMS program and administer my participation (including contacting me) in the ABSTRAL REMS program.

II. Evaluate the appropriate use of ABSTRAL and the effectiveness of the ABSTRAL REMS program.

III. Provide me with educational information with respect to the ABSTRAL REMS program.

IV. Contact my Providers to collect, enter and maintain my Health Information in a secure ABSTRAL REMS database.

V. Make submissions to the FDA, regarding matters such as adverse events and ABSTRAL REMS program effectiveness.

I understand that I am not required to sign this Authorization. However, if I do not sign, I will not be able to enroll in the ABSTRAL REMS program and will not be able to receive ABSTRAL.

I understand that I may revoke (withdraw) this Authorization at any time by faxing a signed, written request to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424). ProStrakan shall notify my Providers and Insurers of my revocation, who may no longer disclose my Health Information to ProStrakan once they have received and processed that notice. However, revoking this Authorization will not affect ProStrakan's ability to use and disclose my Health Information that it has already received to the extent permitted under applicable law. If I revoke this Authorization, I will no longer be able to participate in the ABSTRAL REMS program to receive ABSTRAL.

ProStrakan agrees to protect my information by using and disclosing it only for the purposes described.

This form is required and approved by the FDA as part of the ABSTRAL REMS

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ABSTRAL® (fentanyl) sublingual tablets; FDA required restricted distribution program

Dear Outpatient Pharmacy

ProStrakan, Inc. would like to inform you of the approval of ABSTRAL (fentanyl) sublingual tablets. Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is only available through the FDA mandated ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

In order for an outpatient pharmacy to take part in the ABSTRAL REMS program, and dispense ABSTRAL, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Ensure the pharmacy enables their pharmacy management system to support communication with the ABSTRAL REMS system.
- Re-enroll every two years

To enroll in the ABSTRAL REMS program, visit www.abstralrems.com or call 1-888-ABSTRAL (1-888-227-8725).

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.

3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products. Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in

those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

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.

Medication Guide

It is an FDA requirement to distribute a copy of the enclosed Medication Guide to each patient with each prescription filled for ABSTRAL. A Medication Guide will be provided with every carton of ABSTRAL. If you require additional Medication Guides you can:

- **Print copies from the ABSTRAL website, www.abstral.com.**
- **Print copies from the ABSTRAL REMS program website, www.abstralrems.com.**
- **Contact the ABSTRAL REMS program on 1-888-ABSTRAL (1-888-227-8725).**

Adverse Event Reporting

Prescribers should report all adverse events associated with the use of ABSTRAL directly to ProStrakan at 1-888-ABSTRAL (1-888-227-8725).

If you have questions about ABSTRAL or the ABSTRAL REMS program, please visit www.abstralrems.com for more information or call the toll-free number, 1-888-ABSTRAL (1-888-227-8725).

Thank you,

The ABSTRAL REMS Team.

This letter is required and approved by the FDA as part of the ABSTRAL REMS program.

The ABSTRAL REMS program Dear Inpatient Pharmacy Letter

Important Drug Warning

Subject: Risk of misuse, abuse, addiction and overdose for ABSTRAL® (fentanyl) sublingual tablets; FDA required restricted distribution program

Dear Inpatient Pharmacy:

ProStrakan, Inc. would like to inform you of the approval of ABSTRAL (fentanyl) sublingual tablets. Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is only available through the FDA mandated ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program, a restricted distribution program. If ABSTRAL is prescribed and dispensed to patients in your Healthcare Facility, you must enroll your inpatient pharmacy in the ABSTRAL REMS program.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

In order for an inpatient pharmacy to take part in the ABSTRAL REMS program, and dispense ABSTRAL, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Re-enroll every two years

To enroll in the ABSTRAL REMS program, visit www.abstralrems.com or call 1-888-ABSTRAL (1-888-227-8725).

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Important Safety Information

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products. Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

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.

Adverse Event Reporting

Inpatient Healthcare Facilities should report all adverse events associated with the use of ABSTRAL directly to ProStrakan at 1-888-ABSTRAL (1-888-227-8725).

Please see the attached Full Prescribing Information, including boxed warnings, and Medication Guide for important safety information for ABSTRAL.

If you have questions about ABSTRAL or the ABSTRAL REMS program, please visit www.abstralrems.com for more information or call the toll-free number, 1-888-ABSTRAL (1-888-227-8725).

Thank you,

The ABSTRAL REMS Team.

This letter is required and approved by the FDA as part of the ABSTRAL REMS program.

The ABSTRAL REMS program Outpatient Pharmacy Welcome Letter

Dear Outpatient Pharmacy:

Welcome, and thank you for your interest in ABSTRAL® (fentanyl) sublingual tablets and the ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is available only through the FDA mandated ABSTRAL REMS program, a restricted distribution program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting.

Inpatient dispensing of ABSTRAL is detailed in the ABSTRAL REMS program: An Overview for Inpatient Pharmacies, which is available at www.abstralrems.com.

In order for an outpatient pharmacy to take part in the ABSTRAL REMS program, and dispense ABSTRAL, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Ensure the pharmacy enables their pharmacy management system to support communication with the ABSTRAL REMS system.
- Re-enroll every two years

To enroll in the ABSTRAL REMS program, visit www.abstralrems.com or call 1-888-ABSTRAL (1-888-227-8725). To help you understand the ABSTRAL REMS program, materials are included in this kit, including the ABSTRAL REMS PROGRAM:

- Pharmacy Welcome Letter
- An Overview for Outpatient Pharmacies
- Pharmacy Education Program
- Pharmacy Knowledge Assessment Form
- Pharmacy Enrollment Form

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Further copies of all ABSTRAL REMS program documents can be obtained from the ABSTRAL REMS website. For any questions or additional information about ABSTRAL or the ABSTRAL REMS program, feel free to contact the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or online at www.abstralrems.com.

Medication Guide

It is an FDA requirement to distribute a copy of the Medication Guide to each patient with each prescription filled for ABSTRAL. A Medication Guide will be provided with every carton of ABSTRAL.

If you require additional Medication Guides you can:

- Print copies from the ABSTRAL website, www.abstral.com.
- Print copies from the ABSTRAL REMS program website, www.abstralrems.com.
- Contact the ABSTRAL REMS program on 1-888-ABSTRAL (1-888-227-8725).

Please help us in making this program a success by ensuring the appropriate use of ABSTRAL in those patients who need it.

Thank you,

The ABSTRAL REMS Team

This letter is required and approved by the FDA as part of the ABSTRAL REMS program

The ABSTRAL REMS program Inpatient Pharmacy Welcome Letter

Dear Inpatient Pharmacy:

Welcome, and thank you for your interest in ABSTRAL® (fentanyl) sublingual tablets and the ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program.

ABSTRAL is an opioid analgesic 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 regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for at least one week or longer.

Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is available only through the FDA mandated ABSTRAL REMS program, a restricted distribution program. For inpatient administration of ABSTRAL, patient and prescriber enrollment in the ABSTRAL REMS program is not required. Only the inpatient pharmacy is required to be enrolled to order and dispense ABSTRAL. Inpatient pharmacies may not dispense ABSTRAL for outpatient use.

Outpatient pharmacies within the facility providing dispensing services to outpatients have different REMS requirements, in order to dispense ABSTRAL to outpatients including a separate enrollment in the ABSTRAL REMS program (see the ABSTRAL REMS program – An Overview for Outpatient Pharmacies available at www.abstralrems.com).

In order for an inpatient pharmacy to take part in the ABSTRAL REMS program, and dispense ABSTRAL, an authorized Pharmacist must:

- Review the Pharmacy Education Program
- Successfully complete the Pharmacy Knowledge Assessment
- Complete the Pharmacy Enrollment Form
- Re-enroll every two years

To help you understand the ABSTRAL REMS program, materials are included in this kit, including the ABSTRAL REMS program:

- Inpatient Pharmacy Welcome Letter
- An Overview for Inpatient Pharmacies
- Pharmacy Education Program
- Pharmacy Knowledge Assessment Form
- Inpatient Pharmacy Enrollment Form

ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Further copies of all ABSTRAL REMS program documents can be obtained from the ABSTRAL REMS website. For any questions or additional information about ABSTRAL or the ABSTRAL REMS program, feel free to contact the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or online at www.abstralrems.com.

Please help us in making this program a success by ensuring the appropriate use of ABSTRAL in those patients who need it.

Thank you,

The ABSTRAL REMS Team

This letter is required and approved by the FDA as part of the ABSTRAL REMS program.

ABSTRAL® (fentanyl) sublingual tablets

The ABSTRAL REMS Program Outpatient Pharmacy Enrollment Form

I understand that ABSTRAL (fentanyl) sublingual tablets are only available through the ABSTRAL REMS program and I must comply with the program requirements. In addition as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the ABSTRAL Full Prescribing Information and the *Pharmacy Education Program*, and I have completed the *Pharmacy Knowledge Assessment*. I understand the risks and benefits associated with ABSTRAL and the requirements of the ABSTRAL REMS program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing ABSTRAL have been educated on the risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program, as described in the Pharmacy Education Program. This training should be documented and is subject to audit.
3. I understand that ABSTRAL is not bioequivalent with other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products.
4. I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg).
6. I understand the importance of discussing the risks and benefits of ABSTRAL with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the ABSTRAL Medication Guide must be given to the patient or their caregiver each time ABSTRAL is dispensed.
8. I understand that ABSTRAL will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL ABSTRAL prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the ABSTRAL REMS program to dispense ABSTRAL.
11. I understand that ABSTRAL can only be obtained from wholesalers/distributors that are enrolled in the ABSTRAL REMS program.
12. I understand that our pharmacy will not sell, loan or transfer ABSTRAL inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the ABSTRAL REMS program and successfully complete the enrollment requirements every two (2) years.
14. I understand that ABSTRAL is only available through the REMS program. I understand that the pharmacy must comply with the ABSTRAL REMS program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Authorized Pharmacist Signature* _____ **Date** _____

Title _____ **First Name** _____ **Last Name** _____

Phone Number _____ **E-mail** _____

Pharmacy Information

Pharmacy Name _____ **Chain ID** _____

Address _____ **(corporate enrollment only)**

City _____ **State** _____ **Zip** _____

DEA Number _____ **National Provider Identifier (NPI)** _____

Medicaid ID _____ **State Issued** _____

NCPDP Number _____ **Phone** _____

Fax _____ **E-mail** _____

*For corporate pharmacy enrollment this form can be completed and signed by the authorized corporate pharmacy representative. A list of pharmacy sites that have been trained should be provided with this enrollment form. This list should include the required Pharmacy Information detailed above for each pharmacy site. Form continued overleaf

The ABSTRAL REMS program Outpatient Pharmacy Enrollment Form

Preferred email for program communications (Please tick one)

☐ Authorized pharmacist e-mail address ☐ Pharmacy e-mail address

Medicaid ID

Medicaid ID _____ State Issued _____
Medicaid ID _____ State Issued _____
Medicaid ID _____ State Issued _____

Please fax the completed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424).
You will receive a fax or e-mail with instructions of how to submit test transaction(s) to the ABSTRAL REMS program to ensure that your pharmacy management system has been successfully upgraded to allow communication with the ABSTRAL REMS program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email. For questions regarding the ABSTRAL REMS program, call 1-888-ABSTRAL (1-888-227-8725).

The ABSTRAL REMS Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the ABSTRAL REMS Program for ABSTRAL® (fentanyl) sublingual tablets (the "Program"), sponsored by ProStrakan, Inc., ("Program Sponsor") and supported, under the direction of ProStrakan, Inc., by NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") or another pharmacy transaction switch system (collectively, "Switch Systems").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Switch Systems for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Program Sponsor and Switch Systems to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for the Program Drug NDC #'s listed below to Switch Systems via submission of all billing and reversal requests.

Program Drug(s):	Carton	Blister Card
Abstral 100 MCG	NDC # 42747-221-32	NDC # 42747-221-04
Abstral 200 MCG	NDC # 42747-222-32	NDC # 42747-222-04
Abstral 300 MCG	NDC # 42747-223-32	NDC # 42747-223-04
Abstral 400 MCG	NDC # 42747-224-32	NDC # 42747-224-04
Abstral 600 MCG	NDC # 42747-226-32	NDC # 42747-226-04
Abstral 800 MCG	NDC # 42747-228-32	NDC # 42747-228-04

Pharmacy acknowledges that a billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Switch Systems to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Switch Systems and/or its affiliates in connection with the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; and (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program. These reports may contain information aggregated by NCPDP number. In addition, Pharmacy authorizes Program Sponsor and its contractors Switch Systems, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Switch Systems reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR SWITCH SYSTEMS'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR SWITCH SYSTEMS BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT SWITCH SYSTEMS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

This form is required and approved by FDA as part of the ABSTRAL REMS

ABSTRAL® (fentanyl) sublingual tablets

The ABSTRAL REMS Program Inpatient Pharmacy Enrollment Form

I understand that ABSTRAL (fentanyl) sublingual tablets are only available through the ABSTRAL REMS program and I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the ABSTRAL Full Prescribing Information and the *Pharmacy Education Program*, and I have completed the *Pharmacy Knowledge Assessment*. I understand the benefits and risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program, as described in the Pharmacy Education Program.
3. I understand that ABSTRAL is not bioequivalent to other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products.
4. I understand that ABSTRAL is contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose of ABSTRAL for all patients is the lowest dose (100 mcg).
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the ABSTRAL REMS program to dispense ABSTRAL to outpatients.
7. I understand that our inpatient pharmacy is not to dispense ABSTRAL for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with an ABSTRAL prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the REMS program.
9. I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the ABSTRAL REMS.
10. I understand that our pharmacy will not sell, loan or transfer ABSTRAL inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that ABSTRAL can only be obtained from wholesalers/distributors that are enrolled in the ABSTRAL REMS program.
12. I understand that our pharmacy must re-enroll in the ABSTRAL REMS program every two (2) years.
13. I understand that ABSTRAL is available only through the ABSTRAL REMS program. I understand and agree to comply with the ABSTRAL REMS program requirements for inpatient pharmacies.

Authorized Pharmacist Signature _____ **Date** _____

Title _____ **First Name** _____ **Last Name** _____

Inpatient Pharmacy Information

Name _____

Address _____

City _____ **State** _____ **Zip** _____

DEA Number _____ **State Pharmacy License Number** _____

Phone _____ **Fax** _____

Email _____

Please fax the completed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424). You will receive enrollment confirmation via fax or email. For questions regarding the ABSTRAL REMS program, call 1-888-ABSTRAL (1-888-227-8725).

This form is required and approved by FDA as part of the ABSTRAL REMS.

The ABSTRAL REMS program – An Overview for Outpatient Pharmacies

The ABSTRAL REMS Program - An Overview for Outpatient Pharmacies

This booklet is required and approved by FDA as part of the ABSTRAL REMS

What is the ABSTRAL REMS Program?

The ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program is designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are on treatment, to ensure appropriate use of ABSTRAL. 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. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL in an outpatient setting. Inpatient prescribing of ABSTRAL is detailed in the ABSTRAL REMS program: An Overview for Inpatient Pharmacies.

In order to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of ABSTRAL, your pharmacy will need to be enrolled in the ABSTRAL REMS program. Enrollment requires the authorized pharmacist at the pharmacy to complete the ABSTRAL REMS education program and knowledge assessment on behalf of the pharmacy. The authorized pharmacist must acknowledge that they will train all other pharmacy staff involved in the dispensing of ABSTRAL.

The Education Program is available online at the ABSTRAL REMS program website (www.abstralrems.com) or by contacting the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725). Once the education program and knowledge assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to attest to their understanding of the appropriate use of ABSTRAL and adherence to the ABSTRAL REMS program requirements. Supply of ABSTRAL to pharmacies is controlled by enrolled distributors, who will verify current enrollment of the pharmacy in the ABSTRAL REMS program before shipping ABSTRAL. Pharmacies will be required to re-enroll in the ABSTRAL REMS program every two years.

Only enrolled pharmacies will be eligible to purchase or dispense ABSTRAL. In addition, pharmacies can only dispense prescriptions if the patient and the prescriber are enrolled in the ABSTRAL REMS program. Patients will be automatically enrolled in ABSTRAL REMS upon processing of their first ABSTRAL prescription. If the patient and/or the prescriber are not enrolled in the ABSTRAL REMS program, the ABSTRAL prescription will not be authorized by the ABSTRAL REMS program and should not be dispensed to the patient.

Prescribers, pharmacies and patients are required to acknowledge their understanding of the potential risks involved with inappropriate use of ABSTRAL. Prescribers and pharmacies should ensure:

- **Completion of the relevant education program and knowledge assessment, and submission of the relevant enrollment forms to the ABSTRAL REMS program.**
- **Appropriate patient selection.**
- **Completion and submission of a Patient-Prescriber Agreement to the ABSTRAL**

REMS program.

- **That patients are provided with relevant ABSTRAL REMS program materials and educated on the benefits and risks of treatment with ABSTRAL.**

Overview of Steps for the ABSTRAL REMS Program for Outpatient Pharmacies

Step 1 Pharmacy Education, Enrollment & Pharmacy Management Systems

- Review the ABSTRAL REMS Pharmacy Education Program and successfully complete the Pharmacy Knowledge Assessment.
- Ensure the pharmacy enables their pharmacy management system to support communication with the ABSTRAL REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- Complete and sign the Pharmacy Enrollment Form. Re-enroll every two (2) years.
- Receive a secure username and password to be able to access the ABSTRAL REMS program.

Step 2 Training Other Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of ABSTRAL have been trained to only dispense ABSTRAL in accordance with the ABSTRAL REMS program requirements.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Step 3 Enrollment Confirmation

- Confirm the prescriber and patient are enrolled in the ABSTRAL REMS program with each prescription by submitting a pharmacy billing claim from your pharmacy practice management system. Submitting a claim for a patient's first ABSTRAL prescription through the pharmacy management system will automatically enroll that patient in ABSTRAL REMS program.

- If the prescriber or patient enrollment is not validated, contact the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725) for further instruction.

Step 4 Dispensing

- Receive approval and an authorization ID number from the ABSTRAL REMS program and then prepare label and dispense medication.

Step 5 Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of ABSTRAL appropriately.
- Provide a copy of the Medication Guide to the patient with each prescription.

Step 6 Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to ProStrakan by calling 1-888-ABSTRAL (1-888-227-8725).
- Respond to requests for additional information from the ABSTRAL REMS program.

For more information you can call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or visit www.abstralrems.com.

Important Safety Information

Boxed Warnings

WARNINGS: POTENTIAL FOR ABUSE and IMPORTANCE OF PROPER PATIENT SELECTION

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

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

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products. Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

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 the ABSTRAL REMS (**R**isk **E**valuation and **M**itigation **S**trategy). Under the ABSTRAL REMS, healthcare professionals who prescribe to outpatients, outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense and distribute ABSTRAL, respectively. Further information is available at www.abstralrems.com or by calling 1-888-227-8725.

Warnings and Precautions

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 from other fentanyl products. Directions for safely converting patients to ABSTRAL from other fentanyl products are not currently available. (Note: 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.

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

prescription.

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.

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.

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.

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.

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

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.

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.

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.

Cardiac Disease

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

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.

Adverse Reactions

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.

If you have any questions or require additional information or further copies of all ABSTRAL REMS documents, please visit either www.abstralrems.com or www.abstral.com, or call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

www.abstralrems.com
www.abstral.com

The ABSTRAL REMS Program - An Overview for Inpatient Pharmacies

This booklet is required and approved by FDA as part of the ABSTRAL REMS

What is the ABSTRAL REMS Program?

The ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program is designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are on treatment, to ensure appropriate use of ABSTRAL® (fentanyl) sublingual tablets. 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. In order for inpatient pharmacies (e.g. hospitals, hospices, and long-term care facilities) to dispense ABSTRAL for inpatient use only, the inpatient pharmacy must be enrolled in the ABSTRAL REMS program. For inpatient administration of ABSTRAL patient and prescriber enrollment in the ABSTRAL REMS program is not required.

Inpatient Pharmacy Enrollment

An authorized pharmacist representing an inpatient pharmacy in a healthcare facility will need to review the ABSTRAL REMS education program (Pharmacy Education Program) and successfully complete the Pharmacy Knowledge Assessment and enroll the inpatient pharmacy in the ABSTRAL REMS program. The Pharmacy Education Program is available online at the ABSTRAL REMS program website (www.abstralrems.com) or by contacting the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725). Once the education program and knowledge assessment are completed, the authorized pharmacist will attest to their understanding of the appropriate use of ABSTRAL and adherence to the ABSTRAL REMS program requirements, on behalf of their inpatient pharmacy.

Product supply of ABSTRAL to the inpatient pharmacy will be controlled by enrolled distributors. Enrolled distributors will verify current enrollment of the inpatient pharmacy in the ABSTRAL REMS program, before shipping ABSTRAL. Unless enrolled in the ABSTRAL REMS program, the inpatient pharmacy will not be eligible to purchase or dispense ABSTRAL. Inpatient pharmacies (authorized pharmacist) will be required to re-enroll in the ABSTRAL REMS program every two years.

Inpatient Prescribers

Prescribers at inpatient facilities are not required to be enrolled in the ABSTRAL REMS program to have ABSTRAL dispensed to their patients who are being treated on an inpatient basis. If a prescriber wants to discharge a patient with an ABSTRAL prescription, intended to be dispensed by an outpatient pharmacy, the prescriber will be required to enroll in the ABSTRAL REMS program.

Outpatient Pharmacies

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients must also be separately enrolled in the ABSTRAL REMS program and comply with the ABSTRAL REMS program to dispense ABSTRAL to outpatients, (see the ABSTRAL REMS program – An Overview for Outpatient Pharmacies).

Overview of Steps for the ABSTRAL REMS Program for Inpatient Pharmacies

Step 1. Select an Authorized Inpatient Pharmacist

- The representative is authorized by the inpatient pharmacy to establish and oversee the ABSTRAL REMS program requirements within the inpatient healthcare facility.

Step 2. Complete ABSTRAL REMS Education Program

- The authorized pharmacist must successfully complete the ABSTRAL REMS Pharmacy Education Program and Knowledge Assessment.

Step 3. Enroll

- The inpatient authorized pharmacist must enroll in the ABSTRAL REMS program by completing the ABSTRAL REMS program Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years.

- To enroll, access the ABSTRAL REMS program website at www.abstralrems.com. If you are unable to enroll online, please call the ABSTRAL REMS program call center at 1-888-ABSTRAL (1-888-227-8725) for further assistance.

Step 4. Implement

- The inpatient authorized pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the ABSTRAL REMS program.
- The inpatient authorized pharmacist must ensure that inpatient pharmacists are educated on the risks associated with ABSTRAL and the requirements of the ABSTRAL REMS program, as described in the Pharmacy Education Program.
- The inpatient authorized pharmacist must ensure that the inpatient pharmacy does not sell, loan or transfer ABSTRAL inventory to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense ABSTRAL for outpatient use.

Step 5 Monitoring

- Ensure that suspected adverse events including misuse, abuse, addiction and overdose are promptly reported directly to ProStrakan by calling 1-888-ABSTRAL (1-888-227-8725).
- Respond to requests for additional information from the ABSTRAL REMS program.

For more information you can call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or visit www.abstralrems.com

Important Safety Information

Boxed Warnings

WARNINGS: POTENTIAL FOR ABUSE and IMPORTANCE OF PROPER PATIENT SELECTION

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. Consider the potential for abuse when prescribing or dispensing ABSTRAL in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ABSTRAL for any other fentanyl product may result in fatal overdose.

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

ABSTRAL is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to ABSTRAL. Patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose.

When dispensing, do not substitute an ABSTRAL prescription for other fentanyl products. Differences exist in the pharmacokinetics of ABSTRAL compared to other fentanyl products that could result in clinically important differences in the amount of fentanyl absorbed and could result in fatal overdose.

Special care must be used when dosing ABSTRAL. No more than two doses can be taken per breakthrough pain episode. If the breakthrough pain episode is not relieved patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

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

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of the reach of children.

The concomitant use of ABSTRAL with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

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 the ABSTARL REMS (**R**isk **E**valuation and **M**itigation **S**trategy). Under the ABSTRAL REMS, healthcare professionals who prescribe to outpatients, outpatients, pharmacies and distributors must enroll in the program to prescribe, receive, dispense and distribute ABSTRAL, respectively. Further information is available at www.abstralrems.com or by calling 1-888-227-8725.

Warnings and Precautions

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 from other fentanyl products. Directions for safely converting patients to ABSTRAL from other fentanyl products are not currently available. (Note: 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.

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

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.

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.

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.

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.

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

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.

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.

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.

Cardiac Disease

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

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.

Adverse Reactions

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.

If you have any questions or require additional information or further copies of all ABSTRAL REMS documents, please visit either www.abstralrems.com or www.abstral.com, or call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

www.abstralrems.com
www.abstral.com

Dear Patient:

Welcome to the ABSTRAL Risk Evaluation and Mitigation Strategy (REMS) Program.

ABSTRAL® is used to treat breakthrough pain in adult patients (18 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for their constant cancer pain. ABSTRAL is started only after you have been taking other opioid pain medicines for at least one week and your body has become used to them. Your doctor has determined that ABSTRAL (fentanyl) sublingual tablets may help you control your breakthrough pain.

Before you can receive ABSTRAL you must become part of the ABSTRAL REMS program and agree to all program requirements. The ABSTRAL REMS program is required by the Food and Drug Administration (FDA) and is designed to help you understand ABSTRAL and how to use it correctly and safely. It will also tell you about the benefits and risks of taking ABSTRAL and the process for getting your ABSTRAL prescription. You and your doctor will be able to discuss what these benefits and risks mean for you. Your doctor will also explain very carefully how you must take ABSTRAL.

You will review with your doctor the Medication Guide and a document explaining the ABSTRAL REMS program (The ABSTRAL REMS program - An Overview for Patients and Caregivers). Your doctor will provide you with copies of both. You will receive a new copy of the Medication Guide from your pharmacy each time you get a new prescription for ABSTRAL. Please read the Medication Guide completely before you start taking ABSTRAL and each time you get a new prescription because there may be new information. Be sure to share this important information with members of your household and other caregivers.

Your doctor will also explain the ABSTRAL REMS program Patient-Prescriber Agreement which both you and your doctor have to sign before you can receive your first prescription.

Your doctor will submit a copy of this agreement to the ABSTRAL REMS program and give you a copy to keep. Your doctor will provide you with your prescription for ABSTRAL and will be able to help you find pharmacies that are authorized to dispense this medicine.

Please take your prescription to one of these authorized pharmacies. You will be enrolled in the ABSTRAL REMS program when your first ABSTRAL prescription is filled by the Pharmacy. You will also receive counselling at the pharmacy and a further copy of the Medication Guide along with your prescription.

For any questions or additional information about ABSTRAL or the ABSTRAL REMS program, ask you healthcare provider or feel free to contact the ABSTRAL REMS Call Center at 1-888-ABSTRAL (1-888-227-8725) or visit www.abstralrems.com

Thank you,

The ABSTRAL REMS Team

This letter is required and approved by FDA as part of the ABSTRAL REMS.

The ABSTRAL REMS Program - An Overview for Patients & Caregivers

This booklet is required and approved by the FDA as part of the ABSTRAL REMS.

Why is the ABSTRAL REMS program needed?

ABSTRAL® (fentanyl) sublingual tablets is a prescription medicine that contains the drug fentanyl. ABSTRAL is used to manage breakthrough pain in adults with cancer (18 years of age or older) who are routinely taking other opioid pain medicines around the clock for cancer pain. ABSTRAL can cause life threatening breathing problems which can lead to death, especially if you take more than your doctor tells you to take or if it is taken by anyone other than you. The ABSTRAL Risk Evaluation and Mitigation Strategy (REMS) program is designed to ensure the appropriate use of ABSTRAL.

What is the ABSTRAL REMS program?

The ABSTRAL REMS program is a program that provides specific training for doctors and pharmacists to help them select patients for whom ABSTRAL is appropriate. The ABSTRAL REMS program also helps your doctor and pharmacist provide advice and guidance to you on the correct way to use ABSTRAL, including how to store and dispose of ABSTRAL.

ABSTRAL can only be given to you if you are part of the ABSTRAL REMS program. Doctors who prescribe ABSTRAL, and pharmacists who give you your medication, must have been specially trained as part of the ABSTRAL REMS program. Information is kept on each patient who is prescribed ABSTRAL and for each prescription you are given. Your doctor will have talked to you about this before prescribing ABSTRAL for you. Your doctor will explain the Patient-Prescriber Agreement for the ABSTRAL REMS program which you must read and sign before receiving your prescription. After you are part of the program you can start treatment with ABSTRAL.

Overview of Steps for the ABSTRAL REMS Program for Patients

Step 1 Joining the Program

- Your doctor will talk with you about the best way to use ABSTRAL, including the risks and how to store and dispose of ABSTRAL correctly. Your doctor will also review the ABSTRAL Medication Guide with you and give you a copy. Read and keep the Medication Guide.
- Together you and your doctor will complete and sign the ABSTRAL REMS Patient-Prescriber Agreement.
- You will need to complete a new Patient-Prescriber Agreement every 2 years
- Your doctor will submit a copy to the ABSTRAL REMS program.
- Your doctor will also give you a copy and keep a copy in your medical records.

Step 2 Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement your doctor will write you a prescription for ABSTRAL.
- Your doctor can help you find a participating pharmacy to have your ABSTRAL prescription filled, because only pharmacies that are in the ABSTRAL REMS program can dispense ABSTRAL. You can also find a participating pharmacy by calling the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

Step 3 Taking your Prescription to the Pharmacy

- The pharmacy will check to make sure that your doctor is enrolled in the ABSTRAL REMS program so that they are allowed to dispense ABSTRAL to you.
- You will be enrolled in the ABSTRAL REMS Program when your first ABSTRAL prescription is processed at the pharmacy.
- The pharmacy will remind you how to take, store and dispose of ABSTRAL correctly.
- The pharmacy will also give you written information called a Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information you can call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) or visit www.abstralrems.com.

Medication Guide

ABSTRAL® (AB-stral) CII
(fentanyl)
Sublingual Tablets

100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

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

Read this Medication Guide completely before you start taking ABSTRAL, and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Be sure to share this important information with members of your household and other caregivers.

What is the most important information I should know about ABSTRAL?

ABSTRAL can cause life-threatening breathing problems which can lead to death.

1. **Do not take ABSTRAL if you are not opioid tolerant.**

2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** taking ABSTRAL. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Take ABSTRAL exactly as prescribed by your healthcare provider.**
   - 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. **See the Medication Guide section "How should I take ABSTRAL?" and the Patient Instructions for Use at the end of this Medication Guide for detailed information about how to take ABSTRAL the right way.**
4. **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.
5. **Do not** take ABSTRAL for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give ABSTRAL to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

ABSTRAL is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep ABSTRAL in a safe place** to protect it from being stolen. ABSTRAL can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

ABSTRAL is available only through a program called the ABSTRAL REMS 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

What is ABSTRAL?

- ABSTRAL is a prescription medicine that contains the medicine fentanyl.
- ABSTRAL is used to manage breakthrough pain in adults with cancer (18 years of age and older) 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.
- ABSTRAL is a small tablet that is placed on the floor of the mouth under your tongue (sublingual) and allowed to dissolve.
- You must stay under your healthcare provider's care while taking ABSTRAL.
- ABSTRAL is only:
  - available through the ABSTRAL REMS program
  - given to people who are opioid tolerant

It is not known if ABSTRAL is safe and effective in children under 18 years of age.

Who should not take ABSTRAL?

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 your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in ABSTRAL. See the end of this Medication Guide for a complete list of other ingredients in ABSTRAL.

What should I tell my healthcare provider before taking ABSTRAL?

Before taking ABSTRAL, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental health problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse problem or addiction problem, or a family history of a drug abuse problem or addiction problem
- have any other medical conditions
- are pregnant or plan to become pregnant. ABSTRAL may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. ABSTRAL can pass into your breast milk. It can cause serious harm to your baby. You should not use ABSTRAL while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with ABSTRAL. Sometimes, the doses of certain medicines and ABSTRAL may need to be changed if used together.

- **Do not take any medicine while using ABSTRAL until you have talked to your healthcare provider.** Your healthcare provider will tell you if it is safe to take other medicines while you are using ABSTRAL.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, 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.

How should I take ABSTRAL?

Before you can begin to take ABSTRAL:

- Your healthcare provider will explain the ABSTRAL REMS program to you.
- You will sign the ABSTRAL REMS program Patient-Prescriber Agreement form.
- ABSTRAL is only available at pharmacies that are part of the ABSTRAL REMS program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your ABSTRAL prescription filled.

Taking ABSTRAL:

- **Take ABSTRAL exactly as prescribed. Do not take ABSTRAL more often than prescribed.**
- **If you notice that your tablets are a different shape or color,** be sure to check with your pharmacist to make sure you have the right strength of medicine.
- **Do not** suck, chew or swallow the tablet.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to take ABSTRAL the right way.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- You must not use more than 2 doses of ABSTRAL for each episode of breakthrough cancer pain:
    - Take 1 dose for an episode of breakthrough cancer pain.
    - If your breakthrough pain does not get better within 30 minutes after taking the first dose of ABSTRAL, you can take 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 take another dose of ABSTRAL at this time.**
- Wait at least 2 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 2 hours from the time of that

dose to take a dose of ABSTRAL for a **new** episode of breakthrough pain

- If you need to take 2 doses of ABSTRAL for an episode of breakthrough pain, you must wait 2 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 taking 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 take too much ABSTRAL or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while taking ABSTRAL?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how ABSTRAL affects you. ABSTRAL can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using ABSTRAL.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of ABSTRAL?

ABSTRAL can cause serious side effects, including:

1. **Breathing problems that can become life-threatening**. See "What is the most important information I should know about ABSTRAL?"

   - **Call your healthcare provider or get emergency medical help right away if you:**
     - have trouble breathing
     - have drowsiness with slowed breathing
     - have shallow breathing (little chest movement with breathing)
     - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have taken too much ABSTRAL or the dose is too high for you. **These symptoms may**

lead to serious problems or death if not treated right away. If you have any of these symptoms, do not take any more ABSTRAL until you have talked to your healthcare provider.

2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence**. **Do not stop taking ABSTRAL or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of ABSTRAL are:

- nausea
- sleepiness
- headache

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including ABSTRAL and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking ABSTRAL.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ABSTRAL. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about your side effects. You may report side effects to FDA at 1-800-FDA-1088.

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 ProStrakan, Inc., at 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. You can also call the ABSTRAL REMS program at 1-888-227-8725 or visit www.abstralrems.com.

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)

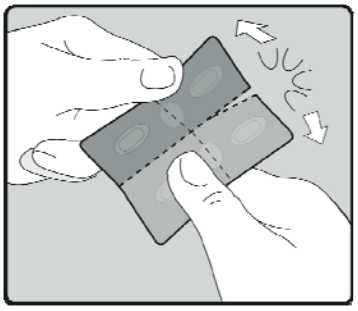


Figure 1

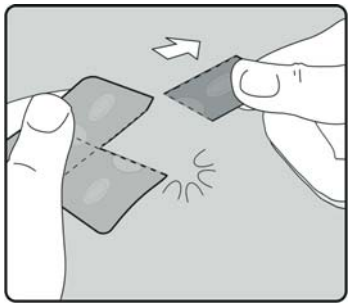


Figure 2

- 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)

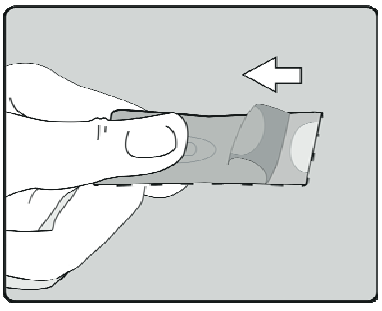


Figure 3

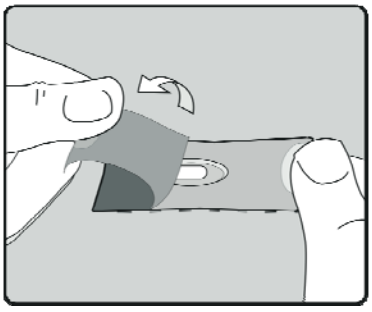


Figure 4

- 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).

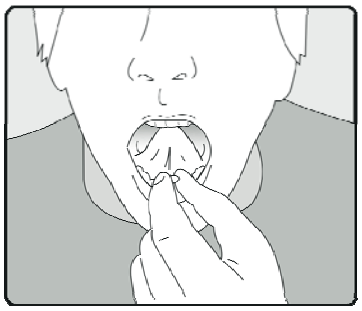


Figure 5

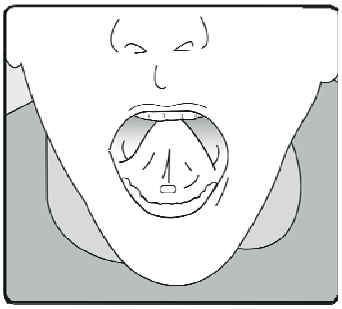


Figure 6

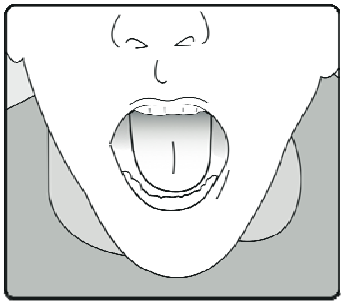


Figure 7

- 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:
Novartis Consumer Health, Inc.,
Lincoln, NE 68517

Manufactured for:
ProStrakan Inc.,
Bedminster, NJ 07921

Issued January 2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ABSTRAL and ProStrakan are trademarks owned by the ProStrakan group of companies.

If you have any questions or require additional information or further copies of all ABSTRAL REMS program documents, please visit either www.abstralrems.com or www.abstral.com, or call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

www.abstralrems.com
www.abstral.com

Dear Distributor

ProStrakan, Inc. would like to inform you of the approval of ABSTRAL® (fentanyl) sublingual tablets. Because of the risk for misuse, abuse, addiction and overdose, ABSTRAL is only available through the FDA mandated ABSTRAL REMS (Risk Evaluation and Mitigation Strategy) program, a restricted distribution program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL.

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. **Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.**
2. **Preventing inappropriate conversion between fentanyl products.**
3. **Preventing accidental exposure to children and others for whom it was not prescribed.**
4. **Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.**

Distributors Responsibilities for the ABSTRAL REMS program

In order to meet the goals of the ABSTRAL REMS, distributors must verify current enrollment of a pharmacy in the ABSTRAL REMS program before distributing ABSTRAL. If the pharmacy is not enrolled, the distributor will not fill any orders for ABSTRAL until enrollment is confirmed. The ABSTRAL REMS program maintains a database of enrolled pharmacies.

As part of the ABSTRAL REMS program, distributors will need to confirm their understanding of the ABSTRAL REMS program as it relates to distributors, by reading and signing the enclosed ABSTRAL REMS Program Distributor Enrollment Form.

Please note that ProStrakan cannot ship ABSTRAL to any distributors who have not completed and signed the Distributor Enrollment Form. Once completed, please fax the enrollment form to the ABSTRAL REMS call center at 1-800-REMS424 (1-800-736-7424) to enable you to start ordering ABSTRAL.

Distributor Overview of Steps for the ABSTRAL REMS Program

Step 1 Distributor Enrollment into the ABSTRAL REMS Program

- Review and understand the requirements of the ABSTRAL REMS program.
- Verify ability to comply with program requirements.
- Verify that relevant staff are trained on the ABSTRAL REMS program procedures.

- Complete the Distributor Enrollment Form (Distributors will be required to re-enroll every two years).
- Fax Distributor Enrollment Form to the ABSTRAL REMS call center at 1-800-REMS424 (1-800-736-7424).
- Receive login information (secure username and password) to access the ABSTRAL REMS program website and the secure ftp site for pharmacy and enrollment verification.

Step 2 Verification of ABSTRAL REMS Program Pharmacy Enrollment Prior to Distributing ABSTRAL

- Obtain the current list of enrolled pharmacies after enrollment by:
  - Downloading (daily) from a secure ftp site
  - Accessing the website (www.abstralrems.com) using a password
  - Calling the ABSTRAL REMS call center on 1-888-ABSTRAL (1-888-227-8725)
- Ensure that pharmacies are enrolled in the ABSTRAL REMS program before distributing ABSTRAL.
- If a pharmacy wants to place an order for ABSTRAL, but is not listed on the enrolled list for the ABSTRAL REMS program, do not distribute ABSTRAL. Instruct the pharmacy that they will need to become enrolled in the ABSTRAL REMS program in order to purchase ABSTRAL.

Step 3 Provide periodic distribution data

- Provide data to the ABSTRAL REMS program including information on shipments to verify shipments to only enrolled pharmacies.

ABSTRAL is available in six strengths, each having a distinctive packaging color and marking.

Product Description	NDC #	Dosage Strength	Unit Size
ABSTRAL® (fentanyl) sublingual tablets	42747-221-32	100 mcg	32 Tablets
	42747-222-32	200 mcg	32 Tablets
	42747-223-32	300 mcg	32 Tablets
	42747-224-32	400 mcg	32 Tablets
	42747-226-32	600 mcg	32 Tablets
	42747-228-32	800 mcg	32 Tablets

Adverse Event Reporting

Distributors should report any adverse events associated with the use of ABSTRAL directly to ProStrakan by calling 1-888-ABSTRAL (1-888-227-8725) or submitting by email to www.abstralrems.com. Please see enclosed Full Prescribing Information for more information about ABSTRAL.

Thank you,

The ABSTRAL REMS Team.

Enclosures: Full Prescribing Information, Distributor Enrollment Form.

This letter is required and approved by FDA as part of the ABSTRAL REMS.

ABSTRAL® (fentanyl) sublingual tablets

The ABSTRAL REMS Program Distributor Enrollment Form

ABSTRAL is available only through a FDA mandated REMS program called ABSTRAL REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program. Under the ABSTRAL REMS program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, and receive ABSTRAL.

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. **Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients**
2. **Preventing inappropriate conversion between fentanyl products**
3. **Preventing accidental exposure to children and others for whom it was not prescribed**
4. **Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose**

Under the ABSTRAL REMS program, distributors must verify current enrollment of a pharmacy in the ABSTRAL REMS program before distributing ABSTRAL to that pharmacy. If the pharmacy is not enrolled, the distributor will not fill any orders for ABSTRAL until enrollment is confirmed. The current list of enrolled pharmacies may be accessed as a daily download from a secure ftp site, from a password protected section of the website (www.abstralrems.com), or by calling 1-888-ABSTRAL (1-888-227-8725) after enrollment.

Distributor Enrollment

I understand that ABSTRAL (fentanyl) sublingual tablets are only available through the ABSTRAL REMS program and I must comply with the program requirements and acknowledge that:

1. I will ensure that relevant staff are trained on the ABSTRAL REMS program procedures and will follow the requirements of the ABSTRAL REMS program.
2. I will ensure that ABSTRAL is only distributed to pharmacies whose enrollment has been validated in the ABSTRAL REMS program.
3. I will provide data to the ABSTRAL REMS program including information on shipment to enrolled pharmacies.
4. I will cooperate with periodic audits or non-compliance investigations to ensure that ABSTRAL is distributed in accordance with the program requirements.

First Name _____ **Last Name** _____ **Title** _____

Authorized Signature _____ **Date** _____

Distributor Name _____

Address _____

City _____ **State** _____ **Zip** _____

DEA Number/ Expiration Date _____

Phone Number _____ **Fax Number** _____

Email Address _____

Please complete this form, sign and fax it to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424).

Please contact the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725) with questions regarding this enrollment form.

This form is required and approved by FDA as part of the ABSTRAL REMS.

The ABSTRAL REMS Program- educational materials printed

Contents

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Welcome and introduction

Welcome to this educational program about ABSTRAL® (fentanyl) sublingual tablets, a medication for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. In this program you will first review the most important safety information about ABSTRAL. You will then be asked to assist a health care prescriber, Dr. Jones, in the process of selecting appropriate patients for treatment with ABSTRAL.

Goals of ABSTRAL REMS

The goals of the ABSTRAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

Indications and Usage

ABSTRAL (fentanyl) sublingual tablets are indicated only for the management of breakthrough pain in cancer patients 18 years of age and older **who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain.**

What Patients are Considered Opioid Tolerant?

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.

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.

Contraindications

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 contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Drug Interactions

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4).

The concomitant use of ABSTRAL with CYP3A4 inhibitors (e.g. certain protease inhibitors, ketoconazole, diltiazem, erythromycin, fluconazole, verapamil) 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.

Dosing and Administration

Start all patients with a single 100 mcg tablet.

Individually titrate ABSTRAL to a dose that provides adequate analgesia with tolerable side effects.

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.

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.

Patients must wait at least 2 hours from taking the last ABSTRAL tablet before treating another episode of breakthrough pain with ABSTRAL.

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.

Limit administration to 4 or fewer breakthrough pain episodes per day.

Administer ABSTRAL tablets by placing 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.

Appropriate Conversion

ABSTRAL is NOT equivalent to any other fentanyl product on a microgram-per-microgram basis.

Differences in the pharmacokinetics of other fentanyl products can result in clinically important differences in absorption and result in fatal overdoses.

When prescribing any transmucosal immediate-release fentanyl product, DO NOT convert from other products without re-titrating according to the prescribing information.

When dispensing any transmucosal immediate-release fentanyl product, DO NOT substitute ABSTRAL for any other fentanyl product.

Patients beginning treatment with ABSTRAL must start titration with the 100mcg dose.

Considerations for Patient Selection

- Patients must be opioid tolerant
- Patients must be aged 18 or older
- Patient use of strong and moderate CYP3A4 inhibitors at the same time as ABSTRAL could lead to fatal respiratory depression
- Patient Risk Factors for ABSTRAL diversion, abuse and addiction include:
  - A personal or family history of alcohol or illicit drug use
  - A history of prescription drug abuse
- Risk Factors for Misuse or Accidental Ingestion by Children include:
  - Children living in the home
  - Children visiting the home
- Young children and teenagers can be at risk of fatal respiratory depression if they accidentally take ABSTRAL.

For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Abuse, Diversion and Addiction

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.** However concerns about abuse, addiction, and diversion must not prevent the proper management of pain.

Patient risk factors for opioid abuse include:

- A history of past or current alcohol abuse
- A history of psychiatric illness
- A family history of illicit drug use

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. 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.

Patient Counselling

Provide patients with a copy of the The ABSTRAL REMS – An Overview for Patients and Caregivers and Medication Guide. The Medication Guide must be provided with all repeat prescriptions.

Advise patients of the serious risks with the inappropriate use of ABSTRAL eg. fatal respiratory depression in opioid non-tolerant patients and of the potential for abuse, misuse and addiction.

Instruct patients and their caregivers that ABSTRAL contains medicine in an amount that could be fatal in children of all ages, in individuals for whom it 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.

Instruct patients never to share ABSTRAL even if they have the same symptoms

Instruct patients that ABSTRAL is only used for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Advise patients that ABSTRAL must only be taken strictly as prescribed, with special regard for dosage and dose titration, and administration route.

Instruct patients that they must continue using their around-the-clock opioid pain medication for cancer pain while talking ABSTRAL.

Advise patients not to switch to ABSTRAL from another fentanyl product without discussing with their physician.

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Accidental Exposure

Accidental exposures can occur in children of all ages, including toddlers through teens.

Accidental exposures can be fatal.

Inform patients that these formulations have a rapid onset.

Talk with your patients about safe and appropriate storage.

Now that you have reviewed the important safety information about ABSTRAL, in the next section you will be introduced to Dr. Jones and her patients. Your task is to assist her in the process of selecting appropriate patients for treatment with ABSTRAL.

Introducing Dr. Jones and her patients

Meet Dr. Jones, the prescriber you're going to be following and six of her patients.

Your task is to help her:
1. Identify the patients for whom ABSTRAL is appropriate.
2. Understand each patient's risk factors.
3. Prescribe ABSTRAL.
4. Counsel her patients.
5. Find the individual patient's effective and tolerable dose (titration).
6. Effectively manage and follow her patients.

To make these decisions you will need to read the Full Prescribing Information and consult the following materials within the booklet:

- **ABSTRAL: Full Prescribing Information**
- **ABSTRAL: Medication Guide**
- **Patient Profiles**
- **The ABSTRAL REMS program: An Overview for Patients & Caregivers**
- **The ABSTRAL REMS program: An Overview for Prescribers**
- **The ABSTRAL REMS program: An Overview for Outpatient Pharmacies**
- **The ABSTRAL REMS program: An Overview for Inpatient Pharmacies**

For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Appropriate Patient Selection

Patient A (Maria): 13 year old female with sarcoma currently receiving chemotherapy with surgery planned, she is using transdermal fentanyl for her underlying persistent cancer pain.

Patient B (Brad): Adult male with advanced lung cancer; his underlying persistent cancer pain has been managed with 25 mcg/hr transdermal fentanyl patches for the past 2 months. He has a history of alcohol and oxycodone abuse.

Patient C (Robin): Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; pain managed with non-steroidal analgesics since discharge from hospital; her pain is no longer adequately controlled.

Patient D (Teresa): Adult female with advanced breast cancer; on long acting morphine (100 mg a day) for 2 weeks but now having episodes of breakthrough pain.

Patient E (Carol): Adult female with advanced breast cancer; on regular oral hydromorphone 5 mg, four times a day (20 mg total) for 3 months and oral transmucosal fentanyl for their breakthrough pain (400 mcg). She has a family of four children living at home with her.

Patient F (Larry): Adult male with chronic back pain but without a diagnosis of cancer. He has been taking opiates regularly for pain and is now experiencing breakthrough pain.

All of Dr. Jones's patients are experiencing breakthrough pain, but ABSTRAL is not an appropriate choice for all of them. On the basis of the Prescribing Information, for which three patients should Dr. Jones **NOT** prescribe ABSTRAL? Select the patients for whom ABSTRAL is not appropriate.

☐ Patient A "Maria" ☐ Patient B "Brad" ☐ Patient C "Robin" ☐ Patient D "Teresa" ☐ Patient E "Carol" ☐ Patient F "Larry"

Answer

ABSTRAL is not appropriate for patients A, C and F. ABSTRAL is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

- Patient A (Maria) is under 18 years.
- Patient C (Robin) is not taking regular opioid therapy and so is not 'opioid-tolerant'. If she took ABSTRAL, she could experience life-threatening side effects such as respiratory depression. Abstral is contraindicated in patients who are not opioid-tolerant and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/daily, or at least 25 mcg transdermal fentanyl/hour, or at least 30 mg of oral oxycodone daily, or at least 8 mg oral hydromorphone daily, at least 25 mg oral oxymorphone daily or an equianalgesic dose of another opioid for a week or longer.
- Patient F (Larry) doesn't have cancer.


Patient A - "Maria"


Patient C - "Robin"


Patient F - "Larry"

For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Appropriate Patient Selection

Patient B (Brad): Adult male with advanced lung cancer; his underlying persistent cancer pain has been managed with 25 mcg/hr transdermal fentanyl patches for the past 2 months. He has a history of alcohol and oxycodone abuse.

Patient D (Teresa): Adult female with advanced breast cancer; on long acting morphine (100 mg a day) for 2 weeks but now having episodes of breakthrough pain.

Patient E (Carol): Adult female with advanced breast cancer; on regular oral hydromorphone 5 mg, four times a day (20 mg total) for 3 months and oral transmucosal fentanyl for their breakthrough pain (400 mcg). She has a family of four children living at home with her.

Dr. Jones has decided that ABSTRAL could be appropriate for Patients B, D and E. But she needs to consider the benefits and risks before prescribing it. Which two patients have risk factors that should be carefully considered before prescribing ABSTRAL?

☐ Patient B "Brad"

☐ Patient D "Teresa"

☐ Patient E "Carol"

Answer

Patients B and E have risk factors that must be carefully considered before prescribing ABSTRAL.

- **Patient B (Brad) has significant risk factors (history of alcohol and drug abuse) that may increase the risk of misuse or abuse of ABSTRAL. Brad should be followed more closely for signs of opioid misuse and abuse.**
  - Additional risk factors to be considered in patients include:
    - A family history of alcohol or substance abuse.
    - History of psychiatric illness.
    - Patients that are current abusers of prescription or illicit drugs are also at increased risk of misuse of ABSTRAL.
- **Patient E (Carol) has children at home so appropriate storage of ABSTRAL in the home is important to prevent accidental exposure. ABSTRAL can be fatal to children or to anyone for whom it was not prescribed.**
  - ABSTRAL must be stored in a safe and secure place and out of the reach of children in all instances, and not just where there are children living at the home. Visiting children and other guests in the home could also pose a risk of ABSTRAL diversion or accidental exposure.

Patient B - "Brad"

Patient E - "Carol"

For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Appropriate Patient Selection

Patient B (Brad): Adult male with advanced lung cancer; his underlying persistent cancer pain has been managed with 25mcg/hr transdermal fentanyl patches for the past 2 months. He has a history of alcohol and oxycodone abuse.

Patient D (Teresa): Adult female with advanced breast cancer; on long acting morphine (100mg a day) for 2 weeks but now having episodes of breakthrough pain.

Patient E (Carol): Adult female with advanced breast cancer; on regular oral hydromorphone 5mg, four times a day (20mg total) for 3 months and oral transmucosal fentanyl for their breakthrough pain (400mcg). She has a family of four children living at home with her.

Dr. Jones has considered the benefits and risks of ABSTRAL for Patients B (Brad), D (Teresa) and E (Carol), and is ready to make a decision about prescribing ABSTRAL. (This is her professional judgment, rather than a recommendation to prescribe in such a situation.) On the basis of the Prescribing Information, what would you advise her to do now?

- ☐ Prescribe ABSTRAL for all three patients
- ☐ Prescribe ABSTRAL for Teresa and Carol but not for Brad (though he would benefit, he might abuse the drug)
- ☐ Determine an appropriate monitoring plan for Brad, to assess for signs of misuse and abuse
- ☐ Warn Carol about the fatal risks to children who accidentally take ABSTRAL. Instruct her how to safely store and dispose of ABSTRAL

Answer

Following her own judgment, Dr. Jones could prescribe ABSTRAL for all three patients.

- But she must consider how best and how often to follow up with Patient B (Brad) for signs of abuse and misuse. 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.
- Patient E (Carol) must be warned about the risks of children taking ABSTRAL and how to keep it in a safe place. ABSTRAL should be kept in a safe place away from children and from anyone for whom it has not been prescribed. ABSTRAL should also be protected from theft. ABSTRAL should be kept in the original blister unit until immediately prior to use. Dispose of any unopened ABSTRAL units remaining from a prescription as soon as you no longer need them. To dispose, remove the ABSTRAL tablets from the blister cards and flush them down the toilet.
- Patient D (Teresa) has no signs of increased risks, but must still be counseled on appropriate use and storage of ABSTRAL.


Patient B - "Brad"


Patient D - "Teresa"


Patient E - "Carol"

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Prescribing ABSTRAL

Patient B (Brad): Adult male with advanced lung cancer; his underlying persistent cancer pain has been managed with 25mcg/hr transdermal fentanyl patches for the past 2 months. He has a history of alcohol and oxycodone abuse.

Patient D (Teresa): Adult female with advanced breast cancer; on long acting morphine (100mg a day) for 2 weeks but now having episodes of breakthrough pain.

Patient E (Carol): Adult female with advanced breast cancer; on regular oral hydromorphone 5mg, four times a day (20mg total) for 3 months and oral transmucosal fentanyl for their breakthrough pain (400mcg). She has a family of four children living at home with her.

Dr. Jones has considered the benefits and risks of prescribing ABSTRAL to her patients. She's decided to prescribe ABSTRAL for Patient B (Brad), D (Teresa) and E (Carol). What are the appropriate next steps?

- ☐ Discuss ABSTRAL and the ABSTRAL REMS program with the patients, review the medication guide and counsel them on the risks and safe use of ABSTRAL
- ☐ Begin titration process for all three patients
- ☐ Check all the other medications they are taking in case of possible drug interactions for example CYP3A4 inhibitors
- ☐ Substitute ABSTRAL for the opiates they are currently taking for their underlying persistent cancer pain
- ☐ Switch Carol (who is currently taking another oral transmucosal fentanyl product for breakthrough pain) to the same dosage of ABSTRAL

Answer

ABSTRAL is indicated for the management of breakthrough pain in opioid tolerant patients therefore, the patient must continue using their around-the-clock opioid pain medication for their constant cancer pain.

The prescriber should discuss ABSTRAL and the ABSTRAL REMS program with the patient and review the Medication Guide.

Patient Counseling:
Before initiating treatment with ABSTRAL, counsel patients and caregivers on ABSTRAL risks and safe use, including:

- The risk for overdose in opioid non-tolerant individuals
- The importance of stopping ABSTRAL if the patient stops taking their around-the-clock opioid pain medicine
- The risk of abuse and addiction
- Do not substitute ABSTRAL for other medication without talking to their doctor first
- The importance of taking ABSTRAL exactly as prescribed and never sharing ABSTRAL. It may harm them or even cause death in individuals for whom it has not been prescribed.
- The need to read the ABSTRAL Medication Guide each time ABSTRAL is dispensed
- The need for appropriate storage and disposal of ABSTRAL

See the ABSTRAL Full Prescribing Information for a complete list of patient counseling messages. The FDA requires that a Medication Guide be dispensed each time ABSTRAL is dispensed. Instruct patients to read the Medication Guide each time ABSTRAL is dispensed because new information may be available.

Titration and Substitution:

- ABSTRAL must be titrated for each patient to find the most effective and tolerable dose.
- The pharmacokinetics of ABSTRAL have differences from those of other fentanyl products so ABSTRAL must not be substituted on a mcg for mcg basis for another fentanyl product as this could lead to overdose.

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Drug Interactions:

- The concomitant use of ABSTRAL with CYP3A4 inhibitor medications may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.
- Dosage modifications should be considered and these patients must be monitored. Common CYP3A4 inhibitors include protease inhibitors (such as ritonavir, used in HIV treatment); macrolide antibiotics and azole antifungals (such as erythromycin and ketoconazole used in bacterial and fungal infections).

Patients taking ABSTRAL at the same time as CYP3A4 inhibitors should be monitored for signs of opioid toxicity and the dose of ABSTRAL managed accordingly.

Titration and dosage

Patient B (Brad): Adult male with advanced lung cancer; his underlying persistent cancer pain has been managed with 25mcg/hr transdermal fentanyl patches for the past 2 months. He has a history of alcohol and oxycodone abuse.

Patient D (Teresa): Adult female with advanced breast cancer; on long acting morphine (100mg a day) for 2 weeks but now having episodes of breakthrough pain.

Patient E (Carol): Adult female with advanced breast cancer; on regular oral hydromorphone 5mg, four times a day (20mg total) for 3 months and oral transmucosal fentanyl for their breakthrough pain (400mcg). She has a family of four children living at home with her.

Dr. Jones starts titration for all three patients. She starts each on 100 mcg tablets. Patients B (Brad) and D (Teresa) respond well – their breakthrough pain subsides within 10 minutes. But Patient E (Carol) still has breakthrough pain after 20 minutes. On the basis of the Prescribing Information, what should Dr. Jones advise Carol to do?

- ☐ Take another 100 mcg immediately
- ☐ Wait an additional 10 minutes (i.e. total of 30 minutes since initial ABSTRAL dose) and if pain is still present, take another 100 mcg
- ☐ Wait another 10 minutes, then if pain is still present, take a 200 mcg tablet.
- ☐ Wait until 2 hours has passed, and then take another 100 mcg

Answer

Carol should wait 30 minutes from the initial ABSTRAL dose, and if the breakthrough pain is not adequately controlled, she can take one more dose of 100mcg. She shouldn't increase the dose for this episode, and she should wait at least two hours before using ABSTRAL to treat another episode of breakthrough pain. The starting dose for the next episode should be 200 mcg of ABSTRAL.

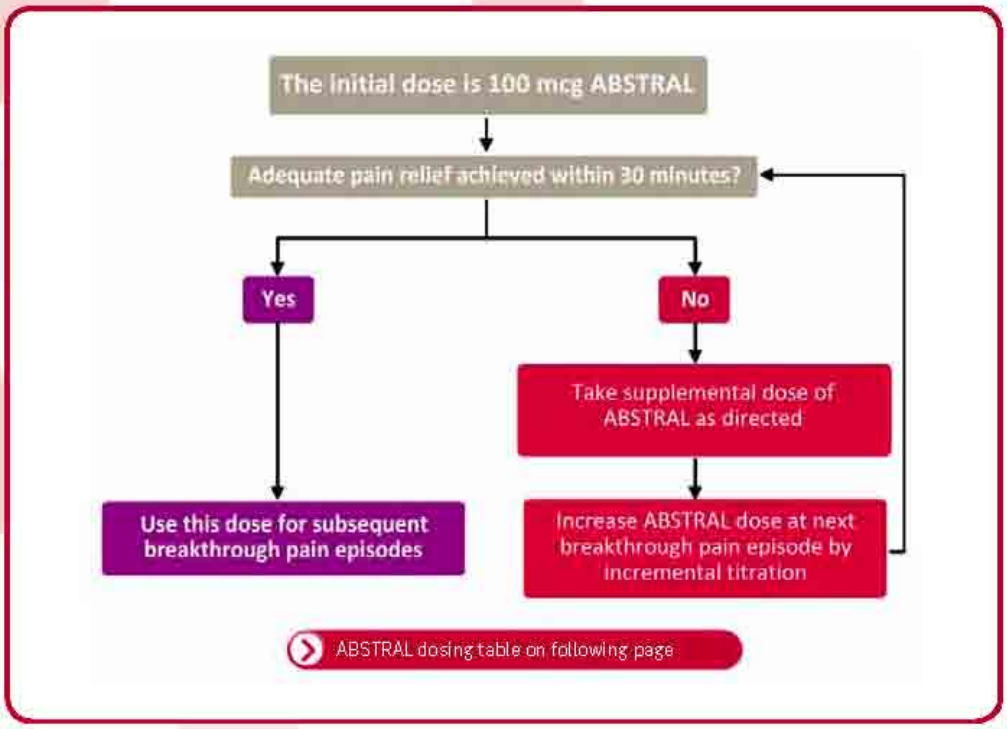
Dr. Jones will also have instructed all patients on how to increase the dose at each subsequent episode if their breakthrough pain is not well controlled, and the patient is having no intolerable side effects. Once a patient has found a dose that controls their breakthrough pain they should use that dose for future episodes.

You can see a diagram of the titration process and the dosage table on the following pages.

ABSTRAL titration process

This chart shows all the steps in the titration process.

The first dose and its supplement (if required) should be 100mcg. However, if pain is uncontrolled the dose for the next episode (and it's supplement, if required) should be increased to 200mcg. At the third episode the dose can be increased to 300mcg and so on, up to the highest dose strength (800mcg). Remember that patients should wait 2 hours from the supplemental dose, between treating episodes of breakthrough pain with ABSTRAL.



ABSTRAL dosage table

The first dose and its supplement (if required) should be 100mcg. However, if pain is uncontrolled the dose for the next episode (and it's supplement, if required) should be increased to 200mcg. At the third episode the dose can be increased to 300mcg and so on, up to the highest dose strength (800mcg). Remember that patients should wait 2 hours from the last ABSTRAL dose before treating the next episode of breakthrough pain with ABSTRAL.

ABSTRAL dose (mcg)	Using
200	2 x 100 mcg tablets, or 1 x 200 mcg tablets
300	3 x 100 mcg tablets, or 1 x 300 mcg tablets
400	4 x 100 mcg tablets, or 2 x 200 mcg tablets, or 1 x 400 mcg tablets
600	3 x 200 mcg tablets, or 1 x 600 mcg tablets
800	4 x 200 mcg tablets, or 1 x 800 mcg tablets

Conclusion

You've now reached the end of this program and you have been provided with information that is essential to prescribe or dispense ABSTRAL safely and appropriately.

You will need to complete the assessment to enroll in the ABSTRAL REMS program in order to have ABSTRAL prescriptions filled. Go to the following page to complete the assessment.

ABSTRAL REMS
Abstral Risk Evaluation and Mitigation Strategy

Knowledge Assessment

You're now going to answer ten questions, which will test your knowledge of appropriate use and prescribing of ABSTRAL® (fentanyl) sublingual tablets.

Once completed, please fill in your details on both pages, tear out the pages and fax to 1-800-REMS424 (1-800-736-7424).

Prescriber / Authorized Pharmacist* Name: _____

Identifier: _____

(DEA Number or Chain ID) _____ ***or Authorized Corporate Pharmacy Representative**

Question 1

The patients described below are all experiencing breakthrough pain, but ONE is not an appropriate patient for ABSTRAL. Which patient should not receive ABSTRAL? *Select one option.*

- ☐ A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
- ☐ B. Adult female with advanced breast cancer; on 60mg of oral morphine daily for the past 4 weeks.
- ☐ C. Adult male with advanced lung cancer, his underlying persistent cancer pain is managed with 25mcg/hour transdermal fentanyl patches for the past 3 months.
- ☐ D. Adult male with multiple myeloma who has bone pain currently managed with 50mg oral oxymorphone daily for the last 2 weeks.

Question 2

The patients described below are experiencing breakthrough pain. ABSTRAL is NOT appropriate for one of them. Which patient should not receive ABSTRAL? *Select one option.*

- ☐ A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
- ☐ B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30mg oral morphine daily for the past 6 weeks.
- ☐ C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100mg oral morphine daily for pain due to bone metastasis.
- ☐ D. Adult female with advanced sarcoma who has been taking a daily dose of 12mg oral hydromorphone for the last three weeks.

Question 3

Certain factors may increase the risk of abuse and/or diversion of opiate medications. Which of the following is most accurate? *Select one option.*

- ☐ A. A history of alcohol abuse with the patient or close family members.
- ☐ B. The patient has a household member with a street drug abuse problem.
- ☐ C. The patient has a history of prescription drug misuse.
- ☐ D. All of the above.

Question 4

A patient is taking another transmucosal fentanyl product (for example Actiq®) but wants to change their medication. His/her doctor decides to prescribe ABSTRAL. How should the prescriber proceed? *Select one option.*

- ☐ A. The prescriber can safely substitute the equivalent dosage of ABSTRAL as it has the same effect as other transmucosal fentanyl products.
- ☐ B. The prescriber must not substitute the equivalent ABSTRAL dose for other transmucosal fentanyl products because they have different absorption properties and this could result in fentanyl overdose.
- ☐ C. Switch from the other transmucosal fentanyl product to ABSTRAL at half the dose.
- ☐ D. The prescriber should base the starting dose of ABSTRAL on the dose of opioid medication used for underlying persistent cancer pain.

Prescriber / Authorized Pharmacist* Name: _____

Identifier: _____

(DEA Number or Chain ID)_____*or Authorized Corporate Pharmacy Representative

Question 5

A patient is starting titration with ABSTRAL. What dose must they start with? *Select one option.*

- ☐ A. 100 mcg
- ☐ B. 200 mcg
- ☐ C. 400 mcg
- ☐ D. 300mcg

Question 6

A prescriber has started titrating a patient with 100 mcg of ABSTRAL. However, after 20 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? *Select one option.*

- ☐ A. Take another dose of 100 mcg immediately.
- ☐ B. Wait 10 minutes (i.e. total of 30 minutes since initial ABSTRAL dose), then, if pain is still present, take another 100 mcg.
- ☐ C. Wait two hours, then, if pain is still present, take another 100 mcg.
- ☐ D. Double the dose to 200mcg and take immediately.

Question 7

A patient is taking ABSTRAL and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true? *Select one option.*

- ☐ A. The patient can't be prescribed erythromycin, because using it at the same time as the other drug could be fatal.
- ☐ B. Use of ABSTRAL with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
- ☐ C. There is no possible drug interaction between CYP3A4 inhibitors and ABSTRAL.
- ☐ D. The dose of ABSTRAL must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8

The ABSTRAL Medication Guide contains important information for the patient and caregiver. Which one of the following statements is most accurate? *Select one option.*

- ☐ A. The patient must be counseled to read the ABSTRAL Medication Guide with every prescription because important information may have changed.
- ☐ B. It is the Pharmacist's responsibility alone to counsel the patient to read the ABSTRAL Medication Guide.
- ☐ C. The patient should be counseled to read the Medication Guide only on the first ABSTRAL prescription.
- ☐ D. The ABSTRAL REMS program will provide a Medication Guide by mail to the patient after ABSTRAL is dispensed.

Question 9

There is a risk of fatal overdose with inappropriate use of ABSTRAL. Which one of the following answers is most accurate? *Select one option.*

- ☐ A. ABSTRAL can be fatal if taken by children.
- ☐ B. ABSTRAL can be fatal if taken by anyone for whom it is not prescribed.
- ☐ C. ABSTRAL can be fatal if taken by anyone who is not opioid tolerant.
- ☐ D. All of the above.

Question 10

Which one of the following statements is most accurate regarding the safe storage and disposal of ABSTRAL? *Select one option.*

- ☐ A. ABSTRAL should be kept in a safe place and out of the reach of children.
- ☐ B. ABSTRAL should be protected from theft from anyone for whom it was not prescribed.
- ☐ C. Dispose of unused medication by opening the blister packaging and flushing ABSTRAL tablets down the toilet.
- ☐ D. All of the above.


ABSTRAL
REMS
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Abstral
(fentanyl) sublingual tablets
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For more information about ABSTRAL, please see Full Prescribing Information, including BOXED WARNINGS


ABSTRAL
REMS
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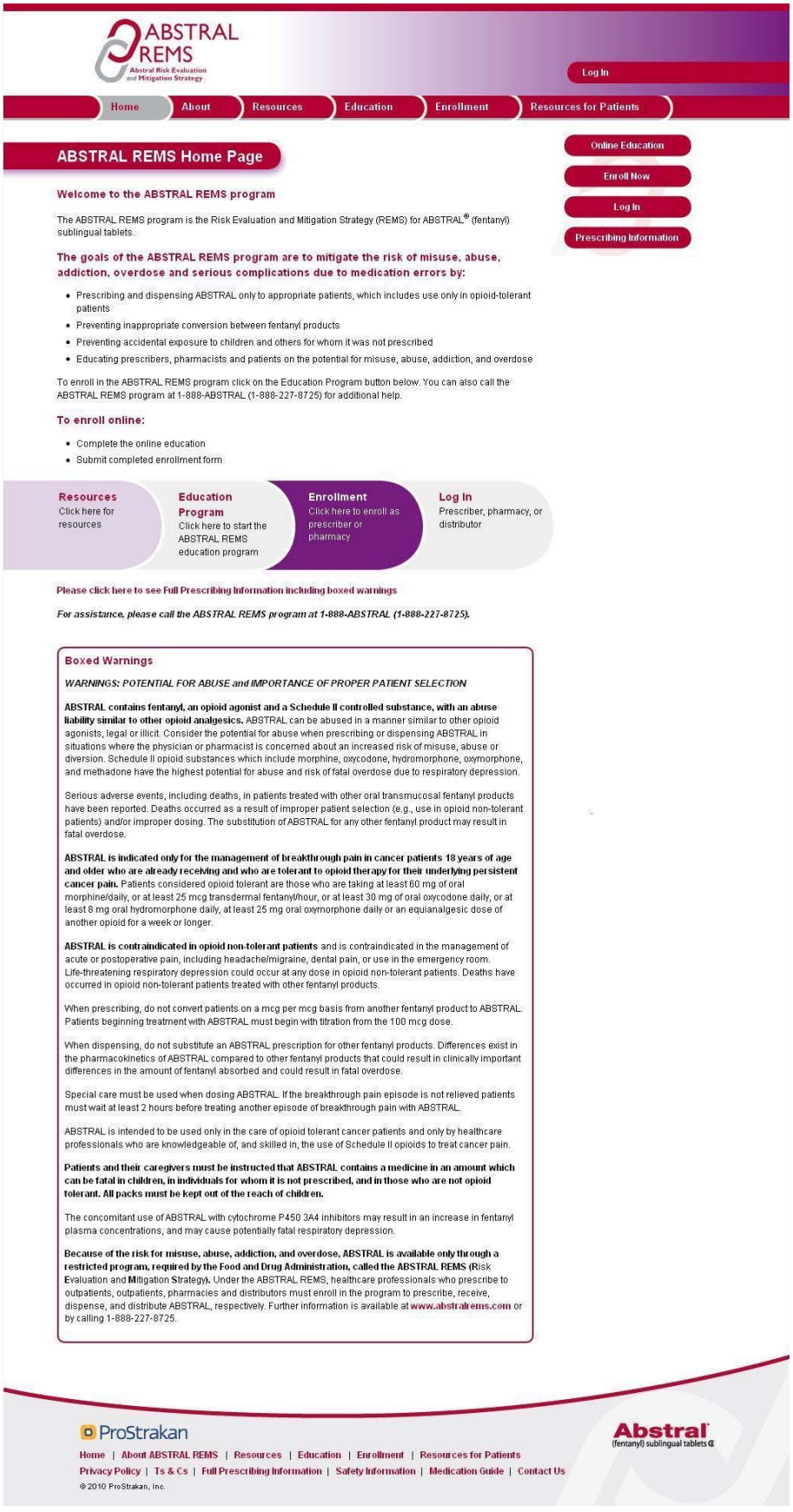
If you have any questions or require additional information or further copies of all ABSTRAL REMS program documents, please visit either www.abstralrems.com, or www.abstral.com or call the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

ProStrakan

www.abstralrems.com
www.abstral.com

The ABSTRAL REMS Program- website



ABSTRAL REMS Frequently Asked Questions (FAQs)

I. ABSTRAL REMS PROGRAM: ALL STAKEHOLDERS FAQs

What is a REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a program established under the Food and Drug Administration Amendments Act (FDAAA) of 2007. FDAAA grants FDA the authority to require a drug manufacturer to develop and implement a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks, while it is marketed.

Links to approved REMS can be found on the FDA website at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

What are the goals of the ABSTRAL REMS Program?

The goals of the ABSTAL REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing ABSTRAL only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

What are the components of the ABSTRAL REMS?

Because of the risk for misuse, abuse, addiction, and overdose, ABSTRAL is available only through a restricted program called the ABSTRAL REMS. Healthcare professionals who prescribe to outpatients, outpatients, pharmacies and distributors must be enrolled in and comply with the ABSTRAL REMS program to prescribe, receive, dispense, and distribute ABSTRAL, respectively.

An overview of the requirements for prescribers, pharmacies, patients and distributors is included below:

- Healthcare professionals, who prescribe ABSTRAL for outpatient use, must review the prescriber educational materials, enroll in the Program, and commit to comply with the REMS requirements.
- To receive ABSTRAL, outpatients must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement with their healthcare provider; outpatients will be enrolled by the pharmacy at the time their first prescription is filled.

- Outpatient pharmacies, that dispense ABSTRAL for outpatient use, must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements.
- Inpatient pharmacies, that dispense ABSTRAL for inpatient use, must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements.
- Wholesalers and distributors, that distribute ABSTRAL must enroll in the Program, and commit to distributing only to authorized enrolled pharmacies.

Healthcare providers who prescribe ABSTRAL for **inpatient use only** are not required to enroll in the ABSTRAL REMS program. Patients in an inpatient setting (e.g. hospitals, hospices, or long-term care facilities) are not required to enroll in the ABSTRAL REMS program.

The ABSTRAL REMS program will provide educational materials to prescribers, and pharmacies. In an outpatient setting, approved medication guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of ABSTRAL.

Why does the ABSTRAL REMS program require prescriber enrollment?

Prescriber enrollment is required to mitigate the risk of misuse, abuse, addiction and overdose of ABSTRAL. ABSTRAL can only be prescribed through the ABSTRAL REMS program, an FDA-mandated REMS program. As part of this restricted distribution program, healthcare providers who prescribe ABSTRAL for outpatient use must be enrolled in the ABSTRAL REMS program for their prescriptions for ABSTRAL to be filled. Healthcare providers who prescribe ABSTRAL for inpatients only are not required to enroll before their ABSTRAL prescriptions are filled.

In order to become enrolled, prescribers must review the ABSTRAL REMS educational materials (Prescriber Education Program) including the Full Prescribing Information and successfully complete the knowledge assessment (Prescriber Knowledge Assessment). Healthcare providers who prescribe ABSTRAL for inpatient use only are not required to be enrolled in the ABSTRAL REMS program.

Why does the ABSTRAL REMS program require pharmacy enrollment?

Pharmacy enrollment is required to mitigate the risk of misuse, abuse, addiction and overdose of ABSTRAL. Only enrolled pharmacies are eligible to receive shipments of ABSTRAL and/or to dispense prescriptions written by enrolled prescribers for outpatients. There must be a designated authorized pharmacist who must review the Pharmacy Education Program and successfully complete the Pharmacy Knowledge Assessment, then complete enrollment on behalf of the pharmacy.

Prescriptions written by prescribers who are not enrolled in the REMS, for outpatient use, will not be authorized by the ABSTRAL REMS program and will not be dispensed to an outpatient.

Healthcare providers who prescribe ABSTRAL for inpatient use only are not required to be enrolled in the ABSTRAL REMS program.

Why does the ABSTRAL REMS program require a Patient-Prescriber Agreement?

The ABSTRAL REMS program requires all prescribers to complete and sign an ABSTRAL REMS Patient-Prescriber Agreement with each new patient, before writing the patient's first prescription. The Patient-Prescriber Agreement ensures that each patient for whom ABSTRAL has been prescribed is appropriately counseled on the safe use and storage of ABSTRAL. The prescriber must keep a copy of the signed Patient-Prescriber Agreement in the patient's chart, give a copy to the patient and submit a copy to the ABSTRAL REMS Program within 10 working days. Once this agreement has been completed, the initial prescription written for the patient may be filled by an enrolled pharmacy. A second prescription for ABSTRAL will not be authorized if a copy of the completed and signed Patient-Prescriber Agreement has not been received by the ABSTRAL REMS program by the time the second prescription is presented to the pharmacy.

A Patient-Prescriber Agreement is not required for inpatient use of ABSTRAL

Where do I find a list of local pharmacies that participate in the ABSTRAL REMS program?

Using the ABSTRAL REMS website, enrolled prescribers and distributors can obtain a list of pharmacies enrolled in the ABSTRAL REMS program by using the feature "Pharmacy Lookup" after they log into the website. This information can also be obtained by calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725).

How can I obtain ABSTRAL REMS materials?

Users can download ABSTRAL REMS materials from the website using Adobe Acrobat Reader version 9.0. The link to this free Acrobat download is available on any web page that has

materials available for download. Materials are also available by calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725) for assistance.

How do I contact the ABSTRAL REMS program?

You can contact the ABSTRAL REMS program by calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725) or by written correspondence to: ProStrakan, Inc., 1430 US Highway 206, Suite 110, Bedminster, NJ 07921-2652.

How should adverse events be reported?

All adverse events associated with the use of ABSTRAL should be reported directly to ProStrakan, Inc. by calling 1-888-ABSTRAL (1-888-227-8725) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

II. ABSTRAL REMS PROGRAM: PATIENT FAQs

As a patient, how do I enroll with the ABSTRAL REMS program?

Before you can be enrolled as an outpatient, you must sign a Patient-Prescriber Agreement with your doctor. Your doctor will go over important information you need to know before you take ABSTRAL.

As an outpatient, you can only be enrolled in the ABSTRAL REMS program through an enrolled pharmacy. When your pharmacist submits your first prescription for ABSTRAL through the pharmacy management system, you will be automatically enrolled in the ABSTRAL REMS program.

Patients in an inpatient setting (e.g. hospitals, hospices, or long-term care facilities) are not required to enroll in the ABSTRAL REMS program in order to be prescribed and dispensed ABSTRAL for inpatient use only.

Where do I find a list of local pharmacies that participate in the ABSTRAL REMS program?

Only pharmacies that are enrolled in the ABSTRAL REMS program can dispense ABSTRAL. Your doctor can help you find a participating pharmacy. You can also get this information by calling the ABSTRAL REMS program at 1-888-ABSTRAL (1-888-227-8725).

III. ABSTRAL REMS PROGRAM: OUTPATIENTPHARMACY FAQs

How does a pharmacy enroll in the ABSTRAL REMS program?

A pharmacy may obtain an enrollment form on-line from the ABSTRAL REMS website (www.abstralrems.com) or by calling 1-888-ABSTRAL (1-888-227-8725) to request delivery of an enrollment package. The package can be delivered to the pharmacy site via courier.

The designated authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the ABSTRAL REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

The designated authorized pharmacist must review the Pharmacy Education Program, successfully complete the Pharmacy Knowledge Assessment and complete the enrollment form through the website, or complete and fax the signed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424). Before a pharmacy is able to dispense prescriptions to outpatients, a signed enrollment form must be received by the ABSTRAL REMS program for each pharmacy requesting enrollment in the program. (See information on pharmacy chain enrollment below).

If the patient's prescription is denied, will the ABSTRAL REMS system explain the reason?

All ABSTRAL prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. A full description of these codes can be found in the program announcement document for pharmacies or by calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725).

How does a pharmacy obtain ABSTRAL from a distributor?

Only enrolled distributors are allowed to distribute ABSTRAL to enrolled pharmacies. The ABSTRAL REMS program provides frequently updated lists of all pharmacies that are currently enrolled in the program for the distributors to verify before distributing ABSTRAL to an enrolled pharmacy.

How does a pharmacy chain enroll in the ABSTRAL REMS program?

An authorized corporate pharmacy representative may complete the ABSTRAL REMS training, knowledge assessment and enrollment on behalf of all their pharmacies within the chain and then document and manage training of all pharmacy staff by the chains' internal processes. The authorized corporate representative would submit a list of all pharmacy sites that have been trained to the ABSTRAL REMS program (with the single enrollment form) for upload into the REMS database.

IV. ABSTRAL REMS PROGRAM: PRESCRIBER FAQs

What is the enrollment process?

The prescriber must successfully complete a Prescriber Education Program, Knowledge Assessment and complete an enrollment form through the website (on-line), or complete and fax the signed enrollment form and knowledge assessment to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424).

A prescriber may obtain an enrollment form on-line from the ABSTRAL REMS website (www.abstralrems.com) or by calling 1-888-ABSTRAL (1-888-227-8725) to request delivery of an enrollment package. The package can be delivered to the prescriber's office via courier.

The program requires that a signed enrollment form and knowledge assessment be received by the ABSTRAL REMS program for each prescriber that requests enrollment. Only healthcare providers who will prescribe ABSTRAL for outpatient use are required to be enrolled in the ABSTRAL REMS program.

Where do I find a list of local pharmacies that participate in the ABSTRAL REMS program?

Using the ABSTRAL REMS website, enrolled prescribers can obtain a list of participating pharmacies in the ABSTRAL REMS program using the feature "Pharmacy Lookup" after logging into the website or by calling 1-888-ABSTRAL (1-888-227-8725).

Can the discussion with the patient on ABSTRAL risks and benefits be conducted by a nurse or other health care professionals.

The program specifically requires that the prescriber conducts and documents the risk benefit discussion with the patient. However, nurses and other qualified health care professionals may still be involved in their standard patient education processes.

Can I write an order for ABSTRAL use with inpatients?

Yes, prescribers can write orders for ABSTRAL for inpatient use only without the prescriber or the patient being enrolled in the ABSTRAL REMS program. However, the inpatient pharmacy needs to be enrolled in the ABSTRAL REMS program in order to receive and dispense ABSTRAL to inpatients in the healthcare facility (e.g. hospitals, hospices, or long-term care facilities).

If a prescriber is discharging a patient with an ABSTRAL prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the ABSTRAL REMS program and complete a Patient-Prescriber Agreement. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the Prescriber's Education Program and enrollment can be obtained through ABSTRAL REMS program (www.abstralrems.com) or by calling 1-888-ABSTRAL (1-888-227-8725).

V. INPATIENT PHARMACY

How do I enroll as an inpatient pharmacy?

To enroll, the inpatient pharmacy must designate an authorized pharmacist, who will complete the required Pharmacy Education Program and Knowledge Assessment for the ABSTRAL REMS program. Upon successful completion of the knowledge assessment, the authorized pharmacist will complete and sign the Pharmacy Enrollment Form through the website (www.abstralrems.com) or complete and fax the signed form to the ABSTRAL REMS program at 1-800-REMS424 (1-800-736-7424).

Additional information about the Pharmacy Education Program and enrollment can be obtained through the ABSTRAL REMS program (www.abstralrems.com) or by calling 1-888-ABSTRAL (1-888-227-8725).

Can inpatient pharmacies obtain ABSTRAL in a Healthcare Facility?

Yes, however, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the ABSTRAL REMS program before inpatient pharmacies can purchase ABSTRAL.

Additional information can be obtained from www.abstralrems.com or by calling the ABSTRAL REMS call centre at 1-888-ABSTRAL (1-888-227-8725).

VI. ABSTRAL REMS PROGRAM: DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in ABSTRAL REMS?

ABSTRAL is only available through a Food and Drug Administration (FDA) mandated Risk Evaluation and Mitigation Strategy (REMS). As part of a restricted distribution REMS program, distributors will need to enroll in the ABSTRAL REMS program in order to be able to purchase and distribute ABSTRAL.

What are the ABSTRAL REMS program requirements for a distributor?

To enroll in the ABSTRAL REMS program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that ABSTRAL is available only through the ABSTRAL REMS program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the ABSTRAL REMS program?

After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure ftp site
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the ABSTRAL REMS website (www.abstralrems.com)
- Calling the ABSTRAL REMS call center at 1-888-ABSTRAL (1-888-227-8725).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
01/07/2011