CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022510Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: January 07, 2011

To: Robert Rappapoert, M.D.
Director, Division of Anesthesia and Analgesia Products (DAAP)

Through: Claudia Karwoski, Pharm.D.
Director, Division of Risk Management (DRISK)
Office of Surveillance and Epidemiology (OSE)

From: **DRISK Scientific Lead**
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Cynthia LaCivita, Pharm.D., Risk Management Analyst (RMA)
Kate Heinrich, M.A., Health Education Reviewer
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Division of Drug Marketing, Advertising and Communications
Mathilda Fienkeng, Regulatory Review Officer (RRO)
Twyla Thompson, RRO
Office of Compliance, Division of Risk Management and Surveillance
Agnes Plante, B.S.N., RN, Consumer Safety Officer,

Subject: **Addendum to: *Final Risk Evaluation and Mitigation Strategy (REMS) Reivew for Abstral (fentanyl) sublingual tablets (Dated December 22, 2010)***

Drug Name (Established Name): ABSTRAL (fentanyl citrate) sublingual tablets

Dosage and Route: Sublingual tablets - 100 mcg, 200, mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg

Application Type Number: NDA 22-510

Applicant: ProStrakan, Inc.

OSE RCM #: **2010 – 2426**

1 INTRODUCTION

The purpose of this review is to amend the Division of Risk Management's (DRISK) review (Reviewer: LaCivita; dated 22 December 2010) of ProStrakan's proposed Risk Evaluation and Mitigation Strategy (REMS) for Abstral (fentanyl citrate) sublingual tablets.

2 DISCUSSION

An individual TIRF REMS will be implemented by the Sponsor for Abstral until a single-shared TIRF REMS has been approved.

At the time of DRISK's December 22, 2010 review, comments on the REMS document and all appended REMS materials were still in the process of being finalized. Therefore, in addition to the revisions requested as part of DRISK's December 22, 2010 review, DRISK and DAAP communicated required revisions (via e-mail) to ProStrakan on December 28, 2010, and on January 03 and 06, 2011 (See DARRTS).

The proposed Abstral REMS, amendment submitted on January 06, 2011 (eCTD Sequence # 0029), includes all the elements put forth in the Agency's TIRF REMS for a shared single system, and addresses all additional required revisions communicated by DRISK and DAAP, to date. The DRISK Review Team finds the proposed REMS for Abstral to be acceptable.

3 RECOMMENDATTIONS

DRISK recommends approval of the Abstral REMS.

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/s/

MEGAN M MONCUR
01/07/2011

CLAUDIA B KARWOSKI
01/07/2011
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 22, 2010
To:	Robert Rappapoert, M.D. Director, Division of Anesthesia and Analgesia Products (DAAP)
Through:	Claudia Karwoski, Pharm.D. Director, Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	**DRISK Scientific Lead** Megan Moncur, M.S., RMA, Acting Team Leader **DRISK Review Team** Cynthia LaCivita, Pharm.D., Risk Management Analyst (RMA) Kate Heinrich, M.A., Health Education Reviewer Marcia Britt, Ph.D., Health Education Reviewer Stephen Sun, M.D., Medical Officer **Division of Drug Marketing, Advertising and Communications** Mathilda Fienkeng, Regulatory Review Officer (RRO) Twyla Thompson, RRO **Office of Compliance, Division of Risk Management and Surveillance** Agnes Plante, B.S.N., RN, Consumer Safety Officer,
Subject:	**Final Risk Evaluation and Mitigation Strategy (REMS) Reivew for Abstral (fentanyl) sublingual tablets**
Drug Name (Established Name):	ABSTRAL (fentanyl citrate) sublingual tablets
Dosage and Route:	Sublingual tablets - 100 mcg, 200, mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg
Application Type Number:	NDA 22-510
Applicant:	ProStrakan, Inc.
OSE RCM #:	**2010 – 2426**

I INTRODUCTION

The Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Risk Management (DRISK) evaluate the proposed Risk Evaluation and Mitigation Strategy (REMS) for Abstral (fentanyl citrate) sublingual tablets.

2 METHODS

- Abstral Proposed REMS, submitted on August 25, 2009 (sequence (seq) no. 0000)
  - REMS Amendment submitted February 1, 2010 (seq no. 0010)
  - REMS Amendment submitted May 28, 2010 (seq no. 0015)
  - REMS correspondence submitted June 1, 20 10 (seq no. 0016)
  - REMS Amendment submitted August 25, 2010 (seq no. 0025)
  - REMS Amendment submitted November 12, 2010 (seq no. 0026)
- Abstral Prescribing Information, submitted December 13, 2010 (seq no.0028)
- DRISK Review of the Risk Evaluation and Mitigation Strategy (REMS) for oral transmuscosal fentanyl citrate and nasal citrate fentanyl spray products. Reviewer: Toyserkani G.A., dated May 13, 2010.
- Clinical Review of Abstral. Reviewer Pucino F., dated March 16, 2010
- Pre-Approval REMS Notification Letter, October 27, 2010

3 BACKGROUND

On August 25, 2009 ProStrakan, Inc. submitted a new drug application (NDA 22-510) for Abstral (fentanyl citrate) sublingual (b) (4) tablets. The proposed indication is 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. Abstral is intended for oral sublingual administration, it should be placed under the tongue immediately after removal from the blister card. The tablet dissolves (b) (4) and appropriate doses should result in a reportable decrease in pain intensity within 30 minutes of drug administration.

Abstral is a member of a group of drugs that the Agency has collectively termed transmucosal immediate release fentanyl (TIRF) products. Actiq, Fentora and Onsolis are approved TIRF citrate products indicated for the management of breakthrough pain in cancer patients in patients who are already receiving and tolerant to opioid therapy. These formulations deliver fentanyl, an opioid agonist and a potent analgesic, rapidly across the oral mucosa. Drug deliver via the oral mucosa eliminates first-pass metabolism that occurs with oral formulations and resulting in increased bioavailability. The rate and maximum plasma concentrations vary considerably between the four drugs, they are not interchangeable therapies. These Schedule II controlled substances have the potential to cause life-threatening respiratory depression at any dose: in patients who are not opioid tolerant; if accidentally consumed by a child or for anyone for whom they were not prescribed; or if used for acute or postoperative pain. It is because of these risks a REMS is required for all of the aforementioned agents.

3.1 Regulatory History for the TIRF

Below is a brief summary of the regulatory history of the approved and marketed TIRF products. For a more in depth review please refer to the review by Toyserkani G.A., dated May 13, 2010.

Actiq (oral transmucosal fentanyl citrate lozenge) was approved November 1998, a RiskMAP was part of the approval. Actiq was identified as a product deemed to have a REMS under section 909(b) of FDAAA. The proposed REMS is currently under review.

Fentora (fentanyl effervescent buccal tablet) was approved September 2006; a RiskMAP was part of the approval. Shortly after approval the Agency received reports of serious adverse reactions, including death due to prescribing in patients who were not opioid tolerant and due to inappropriate substitution with Actiq. Cephalon was notified that a REMS would be required to ensure the benefits outweigh the risks of the drug; the proposed REMS is currently under review.

Onsolis (fentanyl bioerodible mucoadhesive system) was approved July 2009 with a REMS that includes a Medication Guide, communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessment of the REMS. The approved REMS requires prescriber and patient enrollment and distribution of Onsolis through a specialty pharmacy. To date, sales for Onsolis have been low and the program has resulted in shipment delays.

In October 2010 the Agency determined that, in order to minimize the burden to healthcare providers and patients, the TIRFs should have a single shared REMS. ProStrakan (as well as the other innovator and generic sponsors of TIRFs) received a REMS Notification Letter describing the elements of the single shared REMS that could be implemented across all TIRF products. ProStrakan was instructed to revise their proposed REMS to conform to this program. Because the single shared REMS will require substantial time to develop, each sponsor was instructed to develop and implement individual TIRF REMS within six months of receiving the notification letter. The Abstral REMS will be the first TIRF approved and implemented in accordance with the elements laid out in the October 27th, 2010 REMS Notification Letter.

3.2 Pivotal Trials for Abstral

EN3267-005 was the single trial used to support the efficacy of Abstral versus placebo for the treatment of break through pain in patients with cancer who were taking stable doses of opioid medication. To be eligible, patients must be opioid tolerant as defined by the protocol and experience 1-4 episodes of break through pain per day. Patients were screened prior to enrollment, and then began a two-week open-label titration followed by two weeks of double-blinded treatment. In the double-blinded period, patients received 10 doses; 7 were active drug and 3 were matching placebo. The sum pain intensity difference (SPID) was used to compare efficacy with Abstral versus placebo at baseline to 30 minutes. There were 131 patients enrolled in the study, 78 completed the open-label titration and 60 completed the double-blinded randomized period.

Patients who completed the doubled-blind period could proceed to the open-label, 12 month extension study (EN3267-007) to evaluate long-term safety and effectiveness. This study included sixty patients who completed EN3267-005, plus additional 12 patients enrolled under an amendment. Data from SuF-002, EN3267-005 and EN3267-007 trials were integrated for the safety analysis.

3.3 Review of Safety for Abstral

Data from sixteen clinical studies (2 - Phase 3 studies, 1 - Phase 2 studies, and 13 - Phase 1 studies) were integrated for the safety analysis. Many of the patients enrolled in the studies were

very ill and were receiving multiple therapies that included: tranquilzers; muscle relaxants; sedatives; antidepressants; anticonvulsants; benzodiazpeines; and fixed-schedule opioids. For more detailed information please refer to the clinical review by Frank Pucino, Pharm.D, M.P.H., dated March 16, 2010.

3.3.1 *Adverse Events Associated with Opioid Agonists*- Adverse events known to occur with opioid agonists were difficult to study because study patients were taking fixed-schedule opiates in addition to the study drug. As per the clinical reviewer, the major safety findings were as expected considering the patient severity of illness and the concomitant use of fixed-schedule opioids. The most common adverse effects included nausea (22.6%), vomiting (12.2%), and fatigue (11.9%); all are associated with opioid agonists.

3.3.2 *Death*- None were attributed to the study drug. Cancer was the most frequent cause of death.

3.3.3 *Respiratory depression*- Twelve cases were observed in healthy subjects who received 800 mcg as a single dose without naltrexone pretreatment.

3.3.4 *Bradycardia* - one case considered by the investigator to be related to the drug.

3.3.5 *Hepatic Events* – Twenty-five events were reported in multiple-dose study in patients with cancer; none were considered to be related to the study medication.

3.3.6 *Oral Mucosal* – Adverse events that involved the oral mucosa was 24% in the phase III trial. The majority were believed not to be related to the study drug and were reported as mild.

4 PROPOSED REMS FOR ABSTRAL

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/s/

CYNTHIA L LACIVITA
12/22/2010

CLAUDIA B KARWOSKI
12/22/2010
concur

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance

REMS Memorandum

TO:	NDA 22-510
THROUGH:	Suzanne Barone, Ph. D. Team Leader Compliance Risk Management and Strategic Problem Solving Team Division of Compliance Risk Management and Surveillance Office of Compliance
FROM:	Agnes Plante, CSO Compliance Risk Management and Strategic Problem Solving Team Division of Compliance Risk Management and Surveillance Office of Compliance
SUBJECT:	Final memo for Abstral REMS from ProStrakan

This memorandum provides comments from the Office of Compliance (OC) on the final Abstral proposed REMS. These comments provide recommendations for consideration.

Background

Abstral is a fentanyl sublingual tablet formulation designed for oral transmucosal delivery. Abstral contains fentanyl, a potent μ-opioid analgesic with rapid onset of analgesia and short duration of action.

Abstral is one product in the class of transmucosal immediate release fentanyl (TIRF) products. In October 2010 FDA determined that a single, shared system should be used to implement the REMS for all products of the class. In accordance with section 505-1 of the Food Drug and Cosmetic Act (FDCA), the TIRF products are required to submit a risk evaluation and mitigation strategy (REMS) to ensure that the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complication due to medication errors.

FDA devised a REMS program that could be implemented as a single, shared system across all TIRF products. The program includes standardized elements and enrollment forms that can be used by all sponsors of TIRF products and can be implemented using existing pharmacy systems. In October 2010, FDA informed the TIRF sponsors that they would need to revise their proposed REMS to follow the FDA's single shared system program (FDA REMS).

ProStrakan submitted the original REMS August 5, 2009. An amended proposed REMS was submitted on February 1, 2010. During a May 20, 2010 teleconference FDA requested the sponsor revise the February 1, 2010 REMS. The sponsor submitted a revised REMS May 28, 2010 and June 1, 2010. The sponsor submitted a revised REMS August 9, 2010 which incorporated FDA comments. Following a telephone conversation with OND the sponsor submitted a revised REMS August 25, 2010. In October 2010 FDA sent a pre-approval REMS Notification letter to the sponsor outlining the FDA REMS single shared system program. On November 12, 2010 ProStrakan submitted a REMS based on the FDA REMS program.

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.

The REMS consists of a medication guide, elements to assure safe use, implementation system, and a timetable for submission of assessments.

Discussion and Conclusion

OC provided memoranda to OSE/OND for REMS submissions dated August 5, 2009, February 1, 2010, May 28, 2010 and June 1, 2010. The memoranda offered comments and recommendations on the adequacy of the proposed REMS submitted by ProStrakan.

OC made the following recommendations which were incorporated into the FDA REMS single, shared system program:

1. The goals for Abstral needed to be the same as the goals for approved fentanyl product Onsolis. The goals in the FDA REMS are the same for all TIRF products.
2. The distributor information needed to be moved into the implementation system and the language modeled after the approved Onsolis REMS.
3. The language for the timetable for submission of assessments needed to be changed to the standard language. The standard language was included in the FDA REMS.
4. The communication plan needed a time frame for the start and end of distribution. The FDA REMS single, shared system program no longer has a communication plan.
5. There was no information concerning corrective action for non-compliance of prescribers, patients, pharmacies and distributors. A non-compliance action policy was included in the FDA REMS.
6. The call center and website functions needed clarification and detail. The call center and website's functions are clearly defined in the FDA REMS.
7. Prescriber knowledge was not assessed. The FDA REMS incorporated a Prescriber Knowledge Assessment
8. OC had concerns regarding dispensing errors that could be made at the pharmacy due to lack of a hard stop in the computer system. All the sponsors of fentanyl products were encouraged to work together and produce a single shared computer system that would catch errors. Until that system is complete the FDA REMS states that an interim system that uses existing pharmacy management systems that allow for the transmission of REMS information and allows a variety of vendors to participate will be developed by each sponsor.

The Abstral sponsor has addressed all of Office of Compliance's comments by modeling their REMS on the FDA REMS program. Sufficient detail is included in the REMS and supporting document to understand the processes for the implementation of the REMS.

OC finds the proposed Abstral REMS submitted November 12, 2010 acceptable.

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/s/

AGNES R PLANTE
12/20/2010

SUZANNE BARONE
12/20/2010

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

M E M O R A N D U M

DATE: October 27, 2010

TO: File, NDA 22-510
Abstral (fentanyl) sublingual tablets, 100, 200, 300, 400, 600, and 800 mcg
ProStrakan, Inc.

From: Sharon Hertz, M.D.
Deputy Division Director

Through: Bob Rappaport, M.D., Division Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits

of Abstral outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors. In reaching this determination we considered the following:

A. The proposed indication could result in use of the product in a population of (b) (4) patients.
B. The patients for this product are cancer patients with pain that cannot be adequately controlled using around-the-clock oral or transdermal opioids alone. Many of these patients have multiple concurrent complications of their underlying disease and therapy.
C. The expected benefit of the drug to patients is that the delivery system is different than Actiq, Fentora, or Onsolis, the three approved oral transmucosal fentanyl citrate products. Actiq is formulated as a lozenge on a stick with a high sugar content and has been associated with dental caries and elevations in glucose levels in diabetic patients. Fentora is formulated as a tablet that is placed between the mucosa and gum and has caused local ulcers at the site of administration. Onsolis is formulated as a thin film that adheres to the mucosal surface and has not demonstrated either of the two types of adverse reactions noted with Actiq and Fentora. However, it may take up to 15-30 minutes for the film to dissolve, and administration requires several steps (wetting the application area, holding the colored side of the film in place for 5 seconds, avoiding manipulation of the film with the tongue or finger(s), and avoiding liquids for 5 minutes or eating until the film has dissolved). Abstral is formulated as a solid tablet designed for sublingual administration. Dissolution occurs within several minutes, and eating and drinking are permitted once the tablet completely dissolves.
D. The expected duration of treatment with the drug will be from days for the sickest patients who are preterminal, to months for patients with less tumor burden and longer prognoses for survival.
E. The most serious of the known adverse events that are related to the use of an oral tranmucosal fentanyl product include death, respiratory depression and CNS depression which occur primarily if the product is not used properly.
F. Abstral contains the active drug substance fentanyl and is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Abstral. FDA has determined that Abstral poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Abstral. FDA has determined that Abstral is a product for which patient labeling could help prevent serious adverse effects. Furthermore, Abstral has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Abstral.

The elements of the REMS will be a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The following rationale is provided to explain why **inpatient** prescriber training/certification is not required as part of ETASU A of the REMS:

- There are more controls (i.e. established order sets) in the hospital setting to ensure that inpatient prescribers understand the medications they use and choices of medications are limited by hospital formularies (i.e. the majority of hospitals will only have one or two of the TIRF products on their formulary, which will decrease the number of products that can ordered)..
- All pharmacies will be certified/educated and will have access to inpatient dispensing records so they will provide a further control on an inpatient prescriber who places an inappropriate order for a TIRF.
- Inpatient pharmacies will be required to establish order sets or protocols for ordering TIRF products.
- If an inpatient physician who is not enrolled in the REMS program writes an outpatient prescription and the patient takes it to an outpatient/retail pharmacy, the prescription would not be filled.

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Bob A. Rappaport, M.D.
Division Director, Division of Anesthesia and Analgesia Products
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/s/

KIMBERLY A COMPTON
12/08/2010

BOB A RAPPAPORT
12/09/2010

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** 7/15/2010
Abstral (fentanyl citrate)	#22-510	**Comment Set # 1**
DRISK Scientific Lead: - Stephen Sun, MD, Medical Officer - Jeanne Perla, PhD, Risk Management Analyst		**Reviewers and Division Directors:** **DRISK** - Gita Toyserkani, PharmD, Acting Team Leader - Kate Heinrich, MA, Health Education Reviewer - Megan Moncur, Social Scientist, Risk Management Analyst - Claudia Karwoski, PharmD, Division Director **DDMAC** - Mathilda Fienkeng PharmD, Regulatory Review Officer **Office of Compliance Division of Risk Management and Surveillance** - Agnes Plante BSN, RN, Consumer Safety Officer
RCM #: 2009-2066		

Materials Reviewed:

The following revised proposed REMS materials, submitted on May 28, 2010 and June 1, 2010, were reviewed:

1. ABSTRAL REMS (Risk Evaluation and Mitigation Strategy.pdf, 5/28/2010):

2. ABSTRAL REMS Supporting Document (Supporting Document.pdf, 5/28/1010):

3. Prescriber Materials:
   A. Dear Prescriber Introduction Letter (Dear Prescriber Introduction Letter.pdf, 5/28/2010)

   B. ABSTRAL REMS Program - Prescriber Welcome Letter (Dear Prescriber Welcome Letter.pdf, 5/28/2010)
   C. ABSTRAL REMS Program - An Overview for Prescribers (Prescriber (b) (4) Program Overview.pdf, 5/28/2010)
   D. ABSTRAL REMS Program - Prescriber Enrollment Form (Prescriber Enrollment Form.pdf, 5/28/2010)
   E. ABSTRAL REMS Program - Prescriber Enrollment Kit Binder (Prescriber Enrollment Kit Binder.pdf, 5/28/2010)

F. ABSTRAL REMS Program - Prescriber Training Binder (Prescriber Training Binder.pdf, 5/28/2010)
G. ABSTRAL REMS Program - Prescriber Assessment Form (Prescriber Assessment Form.pdf, 5/28/2010)

4. Pharmacist Materials:

A. Dear Pharmacist Introduction Letter (Dear Pharmacist Introduction Letter.pdf, 5/28/2010)
B. ABSTRAL REMS Program - Pharmacy Welcome Letter (Dear Pharmacist Welcome Letter.pdf, 5/28/2010)
C. ABSTRAL REMS Program - An Overview for Pharmacies (Pharmacy [redacted] Program Overview.pdf, 5/28/2010)
D. ABSTRAL REMS Program - Pharmacy Enrollment Form (Pharmacy Enrollment Form.pdf, 5/28/2010)
E. ABSTRAL REMS Program - Pharmacy Enrollment Kit Binder (Pharmacy Enrollment Kit Binder.pdf, 5/28/2010)
F. ABSTRAL REMS Program - Pharmacy Training Binder (Pharmacy Training Binder.pdf, 5/28/2010)
G. ABSTRAL REMS Program - Pharmacy Assessment Form (Pharmacy Assessment Form.pdf, 5/28/2010)

5. Patient Materials:

A. ABSTRAL REMS Program - Patient Welcome Letter (Dear Patient Welcome Letter.pdf, 5/28/2010)
B. ABSTRAL REMS Program - Patient Enrollment Form (Patient Enrollment Form.pdf, 5/28/2010)
C. ABSTRAL REMS Program - An Overview for Patients and Caregivers (Patient/Caregiver [redacted] Program Overview.pdf, 5/28/2010)
D. ABSTRAL REMS Program - Patient Enrollment Kit Binder (Distributor Enrollment Kit Binder.pdf, 5/28/2010)

6. Distributor Materials:

A. Dear Distributor Introduction Letter (Dear Distributor Letter.pdf, 5/28/2010)
B. ABSTRAL REMS Program - Distributor Enrollment Form (Distributor Enrollment Form.pdf, 5/28/2010)
C. ABSTRAL REMS Program - Distributor Enrollment Kit Binder (Distributor Enrollment Kit Binder.pdf, 5/28/2010)

7. Educational/Training Materials:

A. ABSTRAL REMS Educational Materials for Prescribers and Pharmacists (Educational Materials Education and Assessment.pdf, 6/1/2010)
B. Abstral Fact Sheet (Educational Materials Abstral Factsheet.pdf, 6/1/2010)
C. ABSTRAL REMS Fact Sheet (Educational Materials [redacted] Factsheet.pdf, 6/1/2010)
D. Patient Profile Fact Sheet (Educational Materials Patient Profiles Factsheet.pdf, 6/1/2010)

E. Course Transcript (Educational Materials Course Transcript.pdf, 6/1/2010)

8. ABSTRAL REMS Program Website:

A. ABSTRAL REMS Program Website ([redacted] Program Website.pdf, 6/1/2010)

9. ABSTRAL REMS Assessment Materials:

A. NDA Amendment 0010 (Survey Protocol.pdf, 2/1/2010)

10. Additional ABSTRAL REMS Correspondence:

A. NDA Amendment 0010 (Call Center Description.pdf, 2/1/2010)
B. NDA Amendment 0020 (Response to Information Request.pdf, 6/18/2010)

Introduction:

This interim review provides DRISK's preliminary comments on the amended proposed REMS for Abstral (fentanyl citrate) submitted on May 28, 2010. ProStrakan submitted a proposed REMS with the original application on August 5, 2009. An amended proposed REMS was submitted on February 1, 2010. Following a May 20, 2010 teleconference between the Agency and the Sponsor, two major REMS deficiencies were discussed:

a. The proposed REMS lacks safeguards preventing the use of Abstral in non-opioid tolerant patients.

b. The proposed REMS lacks safeguards preventing the pharmacist from dispensing Abstral without first confirming that the patient and prescriber are enrolled in the ABSTRAL REMS Program.

The Review Team requested the Sponsor to revise the currently submitted REMS to include the following information:

1. Provide information on how the REMS will provide safeguards to prevent the use of Abstral in non-opioid patients.

2. Provide information on how the REMS will provide safeguards to prevent the pharmacist from dispensing Abstral prior to confirming the patient is eligible.

3. Update the current proposed REMS to permit in-patient access to drug.

The sponsor submitted an amended proposed REMS on May 28, 2010. The sponsor has not addressed in-patient access in this submission as was requested in the May 20, 2010 teleconference. Please forward below comments to the sponsor and copy DRISK on the correspondence. Let us know if you would like a meeting to discuss these comments before sending to the sponsor.

Comments for the Sponsor:
Please respond to these comments within 2 weeks of receipt to prevent the delay of the review.

General REMS Comments:

1. Based on the teleconference on May 20, 2010, discussion of ABSTRAL use in an in-patient setting, such as an In-patient Healthcare Facility (hospital, long-term care, hospice), was initiated and the subsequent action was to update the REMS proposal to reflect this expansion. However, upon review of the May 28, 2010, no reference was made in the REMS or its Supporting Documents. Provide details to deployment in these settings.

2. According to DDMAC, (b) (4) suggests an inappropriate and potentially misleading perception (b) (4) We recommend replacing the phrase (b) (4) with "ABSTRAL REMS" to facilitate easy recognition of the REMS program with the respective product and to reinforce the purpose of the safety program.

3. All materials should use common terminology throughout the submitted documents and the respective referenced file names. For example, use "Prescribers" consistently throughout the REMS document, the Supporting Document, and any related communications, including exact referenced document file names. Use "Prescriber Enrollment Form" in the document and name the attachment "Prescriber Enrollment Form.pdf" to minimize confusion.

4. How does the Pharmacist confirm that the patient is opioid-tolerant, particularly if the patient uses other pharmacies? What provisions are made if it is not the patient who drops off the prescription or picks up the dispensed drug to answer such questions?

5. Submit the revised Proposed REMS with appended materials and the REMS Supporting Document with a track changes and clean version of all revised materials and documents. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22510	ORIG-1	PROSTRAKAN INC	Abstral (fentanyl citrate) (b) (4) tablets

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/s/

STEPHEN W SUN
07/15/2010

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