CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9 April 2010
From	Robert B. Shibuya, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-510
Applicant	ProStrakan
Date of Submission	5 August 2009
PDUFA Goal Date	30 June 2010 (clock extended for REMS)
Proprietary Name / Established (USAN) names	ABSTRAL (fentanyl sublingual tablet)
Dosage forms / Strength	Sublingual tablet/100, 200, 300, 400, 600, 800 mcg
Proposed Indication(s)	For the relief of breakthrough pain in opioid-tolerant cancer patients
Recommended:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Frank Pucino, PharmD, MPH
Statistical	Yan Zhou, Ph.D. Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D. R. Daniel Mellon, Ph.D.
CMC Review	Muthukumar Ramaswamy, Ph.D. Prasad Peri, Ph.D.
Clinical Pharmacology Review	Zhihong Li, Ph.D. Suresh Doddapaneni, Ph.D.
DSI	Susan Liebenhaut, M.D. Tejashri Purohit-Sheth, M.D.
OSE/DRISK	Steve L. Morin, RN, BSN (Med Guide) Claudia Karwoski Jeanne Perla, Ph.D. (REMS)
OSE/DMEPA	Lori Cantin, R.Ph. Kristina Arnwine, PharmD Denise Toyer, PharmD Carol Holquist, RPh

1. Introduction

ABSTRAL is a sublingual tablet that contains fentanyl. The Applicant, ProStrakan, seeks an indication of the management of breakthrough pain in opioid-tolerant cancer patients. The Applicant proposes to market strengths of 100 to 800 mcg.

Actiq, (fentanyl citrate) oral transmucosal lozenge, approved in 1998, Fentora (fentanyl buccal tablet), approved in 2006, and Onsolis (fentanyl buccal soluble film), approved in 2009, have the same indication. While ABSTRAL is bioequivalent to Actiq, it uses a different route of administration, sublingual, versus absorption across the buccal mucosa.

The products that have followed Actiq have referenced the Agency's previous finding of efficacy and safety for Actiq so the development program for these products is relatively modest. One efficacy study has been required along with a safety database in the range of 300 patients.

ABSTRAL was tested in a single adequate and well-controlled study using what has become the standard design for these products. Opioid-tolerant cancer patients with breakthrough pain complete an open-label dose-finding period. If a successful dose (adequate balance between analgesia and tolerability) is found, the patient enters a 10-period, double-blind, placebo-controlled period. Sequential doses (7 active and 3 placebo, distributed randomly) are administered upon the start of an episode of breakthrough pain and the pain intensity is graded at close intervals. Episodes treated with ABSTRAL had a statistically significant larger summed summed pain intensity difference compared to placebo. The safety database consisted of a total of 694 humans (383 healthy volunteers and 311 patients with cancer). While the safety assessment of this product is confounded (patients are very ill with many concomitant medications and high background opioid use), no unexpected safety signals were observed in the clinical development program.

RISK MANAGEMENT:

The risks of these products have been recognized and anticipated since the initial approval of Actiq, which was approved under Subpart H. However, the Agency's ability to formally manage those risks has increased over the years.

In 2006, when Fentora was approved, the product was subject to a Risk Minimization Action Plan (RiskMAP). The RiskMAP paradigm employed four strategies to manage risk: labeling, education, surveillance, and intervention. The current paradigm for drug product risk management uses the concept of adding more components as the perceived risks of the product increase. From the current perspective of deciding what REMS components are appropriate, the Fentora RiskMAP consisted of the following components: Medication Guide, an educational plan for prescribers and pharmacists, and pharmacovigilance using public health and commercial databases. FDA's options for Sponsor noncompliance with a RiskMAP were

very modest: make public statements, hold an Advisory Committee meeting to discuss the safety of the product, or remove the drug from the market.

Unfortunately, the Actiq and Fentora risk management efforts have been less than fully successful as evidenced by documented prescriptions to patients who are not opioid-tolerant which have resulted in patient deaths. We have also observed evidence of inadequate prescriber education such as the use of the drug in patients with headache, improper dose titration and dose regimen, and improper conversion from other products.

In 2007, the Food and Drug Administration Amendments Act (FDAAA) was passed. Among other changes to the law, this statute authorized Risk Evaluation and Mitigation Strategies (REMS). The minimal REMS element is a Timetable for Submission of Assessments. Other components of REMS that may be required include:

- Medication Guide or patient package insert
- Communication Plan
- Elements to Assure Safe Use (ETASU). Examples of ETASU include:
    - Restricted distribution
    - Certification/attestation of prescribers and pharmacists
    - Mandatory prescriber, pharmacist, or patient education
    - Safe use conditions
    - Required patient monitoring
    - Patient registry
    - Patient counseling
- Implementation System

REMS are enforceable under the statute with civil monetary penalties potentially imposed for noncompliance.

Onsolis, approved in 2009, has an approved, implemented REMS. Highlights of the Onsolis REMS follow:

- Medication Guide (MG)
- Communication Plan
    - Prescribers – Dear Prescriber Letter, package insert (PI) and MG, Prescriber Enrollment Form, Patient Enrollment Form (including Health Insurance Portability and Accountability Act (HIPAA) authorization)
    - Pharmacists – Analogous documents to prescribers
- ETASU
    - Education and enrollment of healthcare providers
    - Counseling and enrollment of patients
    - Restricted distribution, Education and enrollment of specialty pharmacies
- Implementation Plan
    - Education and enrollment of the distributor
    - Maintain a database of enrolled parties
    - Monitor distribution

    - Monitor dispensing by selected, specialty pharmacies
    - Monitor and evaluate ETASU
- Timetable for Assessment – every 6 months for 1 year, then annually

To date, the Onsolis REMS appears to be more successful than the Actiq and Fentora programs although this impression is confounded by very low use of the product (<100 patients as of the writing of this review).

Exactly which components available for REMS should be required in a REMS for a "fentanyl for breakthough cancer pain" product is under internal discussion at the time of finalization of this review. However, patient counseling and a "hard stop" in the verification of opioid-tolerance of the patient are under strong consideration as necessary components. The ABSTRAL REMS currently under review lacks those features. Thus, ABSTRAL cannot be approved at this time.

2. Background

Fentanyl is a pure mu-opioid agonist and was initially approved in 1968 in an injectable formulation (Sublimaze). The drug substance is highly potent and has a short duration of action. Fentanyl is also highly lipophilic and crosses mucous membranes readily. These features (rapid absorption across the oral mucosa and short duration of action) lend themselves to the treatment of breakthough cancer pain which is defined as a short-duration, crescendo episode of intense, severe pain on top of the underlying chronic pain that many cancer patients develop.

The IND under which ABSTRAL was developed (69,190), was submitted in November 2004. The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) met with the sponsor on three occasions, Pre-IND, End-of-Phase 2, and Pre-NDA, as documented in Dr. Pucino's review. Key points related to the clinical development program include:

- The design of the efficacy study was acceptable.
- The safety database should consist of at least 300 patients, of which at least 100 are treated for at least 3 months.
- One efficacy study would suffice to support a NDA.

It is important to note that, during the Pre-NDA meeting, the Applicant was explicitly told that the REMS program summarized in the meeting package for the 23 April 2009 Pre-NDA meeting was not adequate. The Applicant was warned that the REMS submitted with the NDA must be complete and final with the exception of final labeling and artwork. The meeting minutes contain detailed templates for the REMS and the REMS Supporting Documents.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Muthukumar Ramaswamy, Ph.D. with concurrence by Prasad Peri, Ph.D.

The drug substance, (b) (4), is fentanyl citrate (b) (4). The ABSTRAL formulation includes mannitol, (b) (4), croscarmellose, (b) (4), silicified microcrystalline cellulose, (b) (4), and magnesium stearate, (b) (4). None of the drug product components are novel. The tablets are distinguished by strength by debossing of the first number of the strength and shape (round, oval, triangular, diamond-shaped, D-shaped, and capsule-shaped.

The tablets are blister-packed, four to a card.

At the time of finalization of this review, one inspection is pending (b) (4) Pending an adequate inspection (b) (4), Drs. Ramaswamy and Peri have recommended approval for this NDA.

Please see Dr. Ramaswamy's excellent review for further details.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Elizabeth A. Bolan, Ph.D. with supervisory concurrence by R. Daniel Mellon, Ph.D..

As a 505(b)(2) application, the Applicant was able to adequately address Pharmacology/Toxicology (P/T) requirements with a modest P/T program. The Applicant submitted one single-dose oral toxicology study in dogs that had findings consistent with a mu-opioid agonist. The Applicant confirmed that the oral bioavailability of fentanyl is very low in rats and dogs in a series of pharmacokinetic studies.

The drug substance manufacturer has reduced the levels (b) (4) to acceptable levels in the drug substance. In addition, the Applicant conducted an Ames test and an in vitro chromosome aberration assay (b) (4) The Ames test was considered invalid. The aberration assay did not cause structural chromosomal aberrations.

The Applicant also conducted 4- and 28-day toxicology studies of the fentanyl and excipients and excipient-alone in the cheek pouches of guinea pigs and hamsters, respectively. The Applicant concluded that the test articles were not irritants. However, Dr. Bolan notes that the guinea pig study was not conducted under Good Laboratory Practices and the excipient levels tested in the hamsters generally did not use worst-case conditions. Dr. Bolan notes that, despite these limitations, ABSTRAL appears to have a relatively low potential for toxicity to the oral mucosa.

Drs. Bolan and Mellon have recommended approval from the P/T perspective.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Zhihong Li, Ph.D. with concurrence by Suresh Doddapaneni, Ph.D.

ProStrakan proposes to market strengths of 100, 200, 300, 400, 600, and 800 mcg. Obviously, during dose-finding, it is not practical to prescribe and dispense all strengths. Thus, a focus of the Applicant's Clinical Pharmacology program has been to determine whether multiples of lower strengths may be used during dose titration. Along with establishing single- and multiple-dose pharmacokinetics and dose proportionality, the other key issues that were explored in the Clinical Pharmacology program have been whether drug product manufactured at different sites behaves similarly and the relative bioavailability to Actiq, the Reference Drug. Table 1, summarizes the key Clinical Pharmacology studies and findings. Please see Dr. Li's excellent review for details.

Table 1: Summary of key Clinical Pharmacology Studies (a total of 13 studies were submitted)

Study #	Objective	Results	Comments
EN3267-010	Comparison of 400 mcg strength manufactured at Orexo vs. Novartis	Products from manufacturing sites are bioequivalent	
EN3267-003	Comparison of one x 800 mcg; two x 400 mcg; four x 200 mcg	All dose regimens produced equivalent Cmax and AUC	
2246-EU-005	Dose proportionality from 100 to 800 mcg	The product is dose proportional.	
EN3267-001	Relative bioavailability to Actiq	The bioavailability of ABSTRAL is approximately twice that of Actiq.	Study was not conducted correctly. The Actiq was discarded after 15 minutes regardless of the amount remaining.
EN3267-012	Relative bioavailability to Actiq (ABSTRAL 800 mcg vs. Actiq 1600 mcg)	Adjusted for dose, ABSTRAL is bioequivalent to Actiq	
EN3267-013	Relative bioavailability to Actiq (both products tested at 800 and 1600 mcg)	ABSTRAL is bioequivalent to Actiq	

Key pharmacokinetic parameters follow in Table 2 from Study 2246-EU-005, a single- and multiple-dose pharmacokinetic study in healthy Japanese subjects.

Table 2: Summary of Key Pharmacokinetic Indices

Pharmacokinetic Parameter [a]	Dose of Fentanyl (µg)							
	n	100 µg	n	200 µg	n	400 µg	n	800 µg[b]
T_{first} (hours)	12	0.25 (0.24-0.41)	12	0.25 (0.10-0.27)	12	0.25 (0.08-0.25)	12	0.08 (0.08-0.25)
T_{max} (hours)	12	0.50 (0.31-2.00)	12	0.87 (0.27-4.00)	12	1.00 (0.50-1.99)	12	0.50 (0.25-1.00)
C_{max} (ng/mL)	12	0.187 (0.0611)	12	0.302 (0.0923)	12	0.765 (0.288)	12	1.42 (0.466)
C_{6h} (ng/mL)	12	0.0432 (0.0128)	12	0.0833 (0.0305)	12	0.206 (0.0848)	12	0.395 (0.206)
AUC_{τ} (hour*ng/mL)	12	0.599 (0.142)	12	1.06 (0.196)	12	2.60 (0.811)	12	4.49 (1.44)
AUC_{0-t} (hour*ng/mL)	12	0.778 (0.266)	12	1.68 (0.49)	12	4.97 (1.88)	12	8.48 (2.88)
AUC_{0-inf} (hour*ng/mL)	12	0.974 (0.332)	12	1.92 (0.525)	12	5.49 (1.93)	12	8.95 (2.97)
$T_{1/2}$ (hours)	12	5.02 (2.58)	12	6.67 (2.01)	12	13.5 (5.03)	12	10.1 (3.42)
Cl/F (L/hour)	12	113 (35.7)	12	112 (31.5)	12	82.9 (32.1)	12	101 (38.8)

Source: Clinical Study Report, 2246-EU-005, page 78/1179

Drs. Li and Doddapaneni are recommending approval from the clinical pharmacology perspective for this product.

6. Clinical Microbiology

Clinical microbiology is not applicable for this product.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Frank Pucino, PharmD, MPH and the primary statistical review was conducted by Yan Zhou, Ph.D. with concurrence from Dionne Price, Ph.D.

As a 505(b)(2) application, a single adequate and well-controlled study was required to support efficacy.

The Applicant submitted Protocol EN3267-005 (Study 005) to support efficacy. As noted earlier, Study 005 consisted of two key parts (patients could also volunteer to roll over into a third part, an open-label safety extension). Eligible patients were opioid-tolerant (requiring ≥60 mg oral morphine equivalents/day) and suffering 1-4 episodes of breakthrough pain per day. Such patients entered an open-label dose finding period. All patients were started with a 100 mcg dose of ABSTRAL. Each breakthrough pain episode was treated. If the test dose resulted in inadequate analgesia, the dose was escalated through the following doses: 200, 300, 400, 600, and 800 mcg. If intolerable side effects were encountered or the patient did not experience adequate analgesia at 800 mcg, the patient was removed from the study. If the first

dose of a dose level was successful (adequate analgesia and tolerable), this dose was repeated. If effective pain relief for all breakthrough pain episodes was achieved with this dose for two consecutive days, the dose was considered to be the patient's titrated dose and the patient entered the double-blind assessment period of the study.

Patients were not allowed to treat episodes at intervals closer than 2 hours and they were instructed to use their pre-existing rescue opioid if the ABSTRAL was ineffective.

In the double-blind period of the study, the patient was dispensed 10 numbered doses. Seven doses were the titrated dose; three were placebo. The placebo doses were randomly scattered throughout the active doses. Upon the onset of an episode of breakthrough pain, patients self-administered the next numbered dose.

Assessments, including pain intensity via an 11-point numerical pain rating scale, were collected pre-dose and 10, 15, 30, and 60 minutes post-dose. The primary efficacy endpoint was the summed pain intensity difference over 30 minutes (SPID30). Amendment #2, approved 7 September 2007 included an interim analysis. Amendment #3, approved 18 December 2007, discontinued patients from entering the double-blind portion of the study; the interim analysis had stopped the efficacy assessment for trial success. Thus, 12 patients who were successfully titrated did not undergo the double-blind assessment period.

A total of 136 patients were screened, 131 entered the open-label titration phase, and 78 successfully titrated to a dose of ABSTRAL between 100 and 800 mcg. A total of 66 patients entered the double-blind portion of the study and 61 patients were used in the Applicant's intention-to-treat population. The discrepancy of five patients was for administrative reasons such as patient not returning study materials or patient being dispensed double-blind study drug but not taking the drug.

The enrolled patient population had a slight female predominance (54 vs. 46%) and a mean age of 53 years (range 21 to 80 years). There was a strong Caucasian predominance (85%). Because race is not known to predict the efficacy or safety of opioids, the Caucasian predominance is acceptable. Dr. Pucino reviewed the protocol violations and concluded that they were not likely to affect the validity of the results.

The statistics team noted that the design might not be balanced with regard to the episodes or period and requested that the Applicant submit analyses of the SPID30 including a fixed effect for episode in the ANOVA model. Dr. Zhou also analyzed the SPID30 with fixed effects for treatment, episode, pooled center, sequence, and a random effect patient. To address the potential of confounding due to the unbalanced treatment allocation scheme, the statistical team requested a permutation test.

Study 005 was successful; the Applicant demonstrated a statistically significant treatment difference in the SPID30, favoring ABSTRAL. The summary statistics for the primary efficacy endpoint are shown in Table 2, below.

Table 2: Study 005, FDA's Primary Efficacy Analysis

SPID30_reviewer	Abstral Sublingual Tablets (N of subjects = 64) (N of episodes = 414)	Placebo (N of subjects = 64) (N of episodes = 177)
LSMEANS (SE)	52 (4)	36 (4)
Difference from Placebo 95% CI	16 (10, 22)	
P-value*	< 0.0001	

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence, pooled center and a random effect patient

Source: Dr. Zhou's review, page 9/16

The Applicant also submitted Study SuF-002, a randomized, double-blind, four-period crossover study comparing placebo, 100, 200, and 400 mcg ABSTRAL in opioid-tolerant cancer patients with breakthrough pain. The Applicant reported that the 400 mcg dose was superior to placebo. This study was not necessary for approval. However, it is not inconsistent with the findings from Study 005.

8. Safety

The review of clinical safety was also conducted by Dr. Pucino.

As noted by Dr. Pucino, the, the assessment of safety for this class of drugs (fentanyl for breakthrough pain) is problematic. First, the patient population that provided a substantial portion of the safety database (patients with advanced cancer) was very ill, primarily due to the malignancy and its treatment but many had other comorbid conditions. Next, patients were on a wide variety of concomitant medications including treatments specific for their malignancy, other comorbid conditions, and around-the-clock opioids. Naturally, this makes distinguishing adverse events due to the study drug very difficult. Third, due to the design of the controlled trial (a 10-period crossover usually finished in a few days), for all intents and purposes, there is no control group for comparison.

A total of 693 patients and subjects were exposed to ABSTRAL in the 16 studies that comprise the development program. Of those persons, 383 were healthy volunteers and 311 were patients with cancer. Patients were treated for a range of 1-405 days.

Major Safety Findings

Because of the nature of the patient population for this product, a substantial number of deaths and serious adverse events (SAEs) were to be expected. There were a total of 29 deaths and 73 patients who experienced one or more SAEs. The deaths and SAEs were related to the underlying malignancy, the patient's comorbidities, or were expected opioid-related adverse events. A total of 66 patients discontinued due to adverse events. Again, the discontinuations

were due to progression of disease or common opioid-related adverse events (nausea, somnolence, vomiting).

Common Adverse Events and Adverse Events of Interest

As noted, the assessment of safety for an oral transmucosal fentanyl citrate is highly confounded due to the fact that the study drug is an opioid being dosed on top of to an extended-release opioid in extremely ill patients. In addition, there is no control group for comparison. The Applicant presented the common adverse events in various tables, varying the data presented by part of study (titration vs. stable-dose) and thresholds for incidences (≥1% and ≥5%). Table 3 shows the adverse events that occurred during maintenance therapy at a rate ≥5%.

Table 3: Adverse events that occurred during maintenance therapy at a rate ≥5%

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

Source: Dr. Pucino's review, page 76/113

The common adverse events were typical for an opioid being dosed in patients with advanced cancer. The single case coded as an accidental overdose (Patient # 561504 in Study 005) was a 51-year-old woman with metastatic breast cancer who was enrolled into the open-label portion of the study on 7 September 2007. Her titrated dose was 100 mcg. During the time she was enrolled in the study, she experienced two large gastrointestinal bleeds that required hospitalization. On presentation for the second GI bleed (b) (6), she has noted to have overdosed on narcotics and lorazepam. At the time of the overdose, she was taking oxycodone, 180 mg, morphine, 30 mg prn, and study drug. The overdose may have been

related to the use of ABSTRAL but her other CNS depressants cannot be ruled out as causative.

Because of the route of administration, oral cavity exams were required of the Applicant and oral complaints are of interest. Dr. Pucino has summarized those findings nicely in his review. Briefly, the mouth was examined in several of the Phase 1 studies as well as the large Phase 3 studies (Studies 005 and 007, an open-label safety study). The vast majority of the oral lesions observed were related to the underlying malignancy (stomatitis and mucositis). There were a very small number of self-limited oral lesions, potentially related to the formulation. In summary, the sublingual tablet does not appear to be associated with significant local toxicity.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for ABSTRAL.

10. Pediatrics

The Applicant requested a waiver for the Pediatric Research Equity Act for patients age 2 years and below because the number of patients available for study is too small. Because the efficacy of opioids may be extrapolated from efficacy in adults, efficacy will not have to be demonstrated in pediatric patients age 3-16 years. However, the Applicant will have to complete a safety and pharmacokinetic study to inform dosing.

11. Other Relevant Regulatory Issues

We requested inspections of two clinical investigators from the Division of Scientific Investigations. The Inspection Summary from Dr. Susan Leibenhaut indicates that there are no findings that would affect the acceptability of the data.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted. The proposed tradename, ABSTRAL was found to be acceptable. DMEPA had a number of comments regarding the instructions for use that will be addressed in the labeling meetings and negotiations.

12. Labeling

Because Onsolis is the most recently approved oral transmucosal fentanyl for breakthrough cancer pain, we have modeled the ABSTRAL labeling on that label. This product does not offer any advantages or disadvantages over the existing products (in fact it is bioequivalent to Actiq). Thus, the review team will be mindful that no comparative claims will be implied or stated in labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response, pending negotiation of an adequate REMS. In addition, the inspection (b) (4) will have to be completed and found acceptable.

- Risk Benefit Assessment

  The Applicant has submitted substantial evidence of efficacy and the safety observed in the clinical development program is appropriate for this class of drugs. However, given the concerns about prescription drug abuse and the specific risks of this class of drug (due to high potency and the pharmacokinetics), a strong REMS is essential prior to approval.

  At this time, the Applicant has not submitted an adequate REMS. Thus, the benefits of this drug do not outweigh the risks at this time.

- Recommendation for Postmarketing Risk Management Activities

  The exact requirements for a REMS for a fentanyl for breakthrough cancer pain are currently under internal review.

- Recommendation for other Postmarketing Study Commitments

  Beyond the requirement for a robust REMS, no other postmarketing study requirements or commitments are necessary.

- Recommended Comments to Applicant

  The Applicant should be advised that it must improve its REMS prior to approval. The Action Letter should also remind this Applicant of the responsibility to fulfill the requirements of PREA.

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/

ROBERT B SHIBUYA
04/13/2010