



NDA 022510

NDA APPROVAL

ProStrakan, Inc.
1430 US Highway 206, Suite 110
Bedminster, NJ 07921

Attention: Dalena DeGrazia, MBA
Director, US Regulatory Affairs

Dear Ms. DeGrazia:

Please refer to your New Drug Application (NDA) dated August 5, 2009, received August 5, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Abstral (fentanyl) sublingual tablets.

We acknowledge receipt of your amendments dated August 7 and 25 (2), September 9 (2) and 29, October 30, November 2 and 3, and December 3, 2009, and February 1, 5, and 19, March 3 and 10, May 28, June 1 (3), June 4, 18, and 22, July 1 and 8, August 9 and 25, November 12, and December 10 and 13, 2010, and January 5, and 6, 2011.

This new drug application provides for the use of Abstral (fentanyl) sublingual tablets 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.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on July 8, (blister) and August 9, 2010 (carton) as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022510.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable. This is because there are too few pediatric patients in this age range who could appropriately use this product and therefore studies would not be feasible.

We are deferring submission of your pediatric study for ages 7 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1718-1 A safety and pharmacokinetic study of sublingual fentanyl tablets (Abstral) for the treatment of breakthrough pain, including cancer pain and pain due to chronic medical conditions, in opioid-tolerant children ages 7-16 years old.

Final Protocol Submission: January 30, 2012
Study/Trial Completion: October 30, 2015
Final Report Submission: January 29, 2016

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated “**Required Pediatric Assessment(s)**”.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated October 27, 2010.

Pursuant to 505-1(f)(1), we have also determined that Abstral (fentanyl) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of overdose, abuse, addiction, and serious complications due to medication errors that are listed in the labeling. The elements to assure safe use will provide for the education of prescribers and patients so that they are aware of the risks associated with the use of Abstral (fentanyl) and about important information regarding how to use the product safely in order to help prevent the serious adverse effects noted above. The elements will also assure proper patient selection and dispensing of Abstral.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on January 6, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. For the assessment of enrollment and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers/distributors, the following data will be tabulated:
 - a. The total numbers and geographic distribution of prescribers enrolled in the ABSTRAL REMS program, number of new prescribers enrolled during the current reporting period, and number of prescribers who were inactivated
 - b. The total numbers and geographic distribution of pharmacies enrolled in the ABSTRAL REMS program, number of new pharmacies enrolled during the current reporting period, and number of pharmacies that were inactivated (reported by type of pharmacy, inpatient or outpatient)

- c. The total numbers and geographic distribution of patients enrolled in the ABSTRAL REMS program, new patients enrolled during the current reporting period, and number of patients who were inactivated
 - d. The number of completed *Knowledge Assessments* for prescribers and authorized pharmacists, and a tabulation of the number of attempts required to successfully complete the *Knowledge Assessment*
 - e. The total number of wholesalers/distributors enrolled in the ABSTRAL REMS program, number of new wholesalers/distributors enrolled during the current reporting period, and number of wholesalers/distributors that were inactivated
2. Dispensing activity for enrolled pharmacies (inpatient and outpatient); including authorization to dispense data from enrolled outpatient pharmacies
 3. For the assessment of program infrastructure and performance:
 - a. A summary and root cause analysis of all unintended system interruptions (e.g., due to system failure, program failure, inaccurate training), including, but not limited to:
 - 1) Barriers or delays in patient access due to:
 - a) False negatives: e.g., all entities are enrolled, but system generated a prescription rejection notice
 - b) Prescriber delay in submitting the completed *Patient-Prescriber Agreements* to the ABSTRAL REMS Program
 - c) Inadvertent enrollment deactivations, or failures to notify enrollees of forthcoming enrollment expirations
 - d) Prescriber who is not aware of ABSTRAL REMS program (i.e., not enrolled) prescribes ABSTRAL
 - e) Geographic barriers: lack of enrolled prescribers and/or pharmacies in a patient's local area
 - f) A report on the length of the delay (i.e., how long it took for patient to receive ABSTRAL after the original prescription was denied by the pharmacy)
 - 2) Inappropriate patient access:
 - a) False positives: e.g., one or all entities were not enrolled but system verified dispensing/generated a unique authorization code
 - b) Inpatient pharmacy dispensing for outpatient use
 - b. An assessment of the process for pharmacies to upgrade their pharmacy management systems, including a report on the time required for outpatient pharmacies to upgrade their

- pharmacy management systems (mean, maximum and minimum amount of time), and on the number of pharmacies that tried and were unable to modify their systems
- c. An evaluation of the enrollment process for prescribers, pharmacists, and wholesalers/distributors, including a summary of the method used to enroll (e.g., online, fax), and a report on the quality of the data received (e.g., number of incomplete forms received)
 - d. Report of reasons for and the number of times a “back-up” system was used to validate a prescription, either due to problems at the pharmacy-level, Switch or with the ABSTRAL REMS database
 - e. Call center report, including a summary of frequently asked questions and problems reported, and any needed program enhancements
 - f. A description of the corrective actions taken based on the programs/system tracking of these occurrences
4. Results of surveys conducted of prescribers’ and pharmacists’ (inpatient and outpatient) understanding and knowledge of the safe use and appropriate prescribing of ABSTRAL, as described in the ABSTRAL REMS educational materials and PI
 5. Results of surveys conducted of patients’ understanding and knowledge of the serious risks and safe use of ABSTRAL
 6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 7. A report on the number of Dear Healthcare Professional letters mailed (prescriber and pharmacy), when the letters were mailed, what information was included in the mailings, and number of returned mailings
 8. Results of any prescriber, pharmacy, wholesaler/distributor, and vendor audits conducted, and corrective actions taken during the reporting period
 9. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
 10. Results of surveillance and monitoring activities for abuse, misuse, and overdose including:
 - a. Signals that indicate misuse, abuse, overdose, or addiction
 - b. Signals that indicate serious adverse events or deaths related to inappropriate prescribing or other prescriber misuse of ABSTRAL, such as patients obtaining prescriptions from multiple prescribers, prescriptions to non-opioid tolerant patients, and prescriptions for inappropriate doses
 11. Drug Utilization Data including the following information:

- a. The number of cumulative initial and continuing prescriptions to date and new initial prescriptions during the reporting period, as well as minimum, maximum, mean and median number of prescriptions per patient
- b. ABSTRAL Month-to-Date Sales (Distribution) Report (by type of pharmacy, inpatient or outpatient)
- c. Data from flagged prescriptions from more than two prescribers to the same patient
- d. An analysis to evaluate ABSTRAL REMS utilization patterns including use in non-opioid tolerant patients

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022510 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022510
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022510**

**REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

EXPIRATION DATING PERIOD

A 36 month expiration date is granted for Abstral (fentanyl) sublingual tablets when stored at 20-25°C (68-77°F), [see USP Controlled Room Temperature].

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Kimberly Compton, Senior Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.

Director

Division of Anesthesia and Analgesia Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

Carton and Container Labeling

REMS

REMS Materials

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