

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022510Orig1s000

CHEMISTRY REVIEW(S)

Abstral (fentanyl) Sublingual Tablets

NDA 22-510

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Prostrakan Inc.
1430 US Highway 206, Suite 110
Bedminster, New Jersey 07921-2652, USA

Indication: For the management of breakthrough pain in opioid-tolerant cancer patients. The original manufacturing process for the tablets was developed at Orexo, Sweden and transferred to Novartis Consumer Healthcare, Nebraska. The drug retains the fast onset and individualized dose-titration aspects of Reference Listed Drug (RLD) Actiq®, NDA 20-747.

Presentations:

Abstral Tablets are available in 100-800 mcg strengths (free base) and packaged in child resistant blisters cards with peelable foil. The tablet strengths are distinguished by debossing of the first number of the strength and shape (round, oval, triangular, diamond-shaped, D-shaped, and capsule-shaped).

100 microgram tablet is a round tablet marked with the number “1”

200 microgram tablet is an oval-shaped tablet marked with the number “2”

300 microgram tablet is a triangle-shaped tablet marked with the number “3”

400 microgram tablet is a diamond-shaped tablet marked with the number “4”

600 microgram tablet is a “D”-shaped tablet marked with the number “6”

800 microgram tablet is a capsule-shaped tablet marked with the number “8”

EER Status: Acceptable 27-April-2010

Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Methods Validation – Will not be requested since none of the methods are novel.
Pharmacology/Toxicology –Acceptable (3/11/10)

Original Submission: 5-Aug-2009

Post-Approval CMC Commitments:

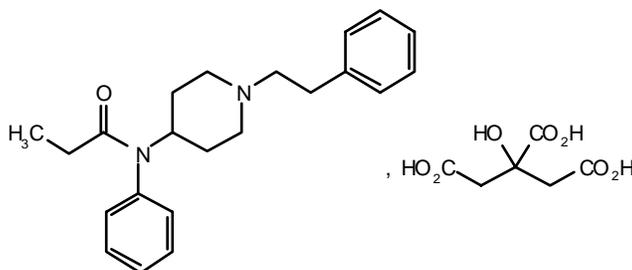
None

Drug Substance:

(b) (4) fentanyl citrate USP ((b) (4)) is a white to off-white powder and is the active ingredient for the tablets. Its chemical name is N-(1-Phenethyl-4-piperidyl)

propionanilide citrate (1:1) and it is a [μ-opioid](#) agonist and is approximately 80 times more potent than [morphine](#). Fentanyl is a scheduled II controlled drug substance, with an abuse liability similar to other opioid analgesics. It is highly lipophilic, freely soluble in organic solvents and sparingly soluble in water (1:40). (b) (4)

The lots of drug substance manufactured (b) (4) have a retest period (b) (4).



The drug substance specifications include Description, Appearance of Solution, ID (IR and HPLC), Assay, Related Substances, Loss on Drying, Residue on Ignition, Heavy Metals, Volatile Compounds, and Particle Size Distribution (PSD). The residual solvent impurities and inorganic impurities in the drug substance are controlled in the manufacturing process by appropriate specification that meets USP monograph for fentanyl citrate.

Conclusion: The drug substance is satisfactory.

Drug Product:

Abstral (fentanyl) sublingual tablets are available in six different strengths 100 (round), 200 (oval), 300 (triangle), 400 (diamond), 600 (D-shaped), and 800μg (capsule) and are readily differentiated by their shape and debossing on one side of the tablets. The 100 μg, 200 μg, 300 μg and 400 μg tablets each weigh 70 mg; 600 μg tablets weigh 105 mg; and 800 μg tablets weigh 140 mg. The tablets disintegrate rapidly when placed under the tongue. The formulation contains mannitol (b) (4), croscarmellose (b) (4), silicified microcrystalline cellulose (b) (4), and magnesium stearate (b) (4). Compendial grade excipients are used in this formulation. Tablets are packaged in child-resistant, protective blister cards with peelable foil. Each blister card contains 4 tablets. Blisters will be packaged in card board cartons in different pack sizes. Two pack sizes, of 12 and 32 tablets, are proposed for 100, 200, 300 and 400 μg strengths. One pack size (32 tablets) is proposed for 600 and 800 μg strengths.

The manufacturing process consists of (b) (4)

This drug product manufacturing process was identified to have QbD elements and a team review was performed. (b) (4) the process development, optimization, and scale-up studies were performed using both the traditional approach and by Design of Experiments (DOE) studies (b) (4)

. Based on development studies, the firm

identified critical unit operations, critical process parameters, in-process controls, and product characteristics for finished product. (b) (4)

Uniformity of the blend was assessed indirectly through content uniformity test by stratified sampling and by uniformity of dosage unit test on finished product (USP <905>) during validation. (b) (4)

The specifications for the finished product include testing for Appearance, Identification, Assay, Degradation Products, Disintegration Time, Friability, Water Content, Uniformity of Dosage Units, and Microbiological Limits. Dissolution and disintegration were used as a tool to monitor product quality during development. (b) (4)

The Abstral (fentanyl) sublingual tablets are manufactured at Novartis, Lincoln, NE, USA. The proposed commercial batch size (b) (4)

Abstral tablets should be stored at 20-25°C with brief excursion permitted between 15 and 30°C (59 to 89°C) until ready to use. The drug product should be protected from moisture. The tablets have an expiration period of 36 months.

Outstanding issues: None

Conclusion: The drug product is recommended for approval.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval**.

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/

PRASAD PERI
05/17/2010
Recommend Approval

NDA 22-510

ABSTRAL® (Fentanyl) Sublingual Tablets

Prostrakan

Muthukumar Ramaswamy, Ph.D.
Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)

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Executive Summary Section

Chemistry Review Data Sheet

1. NDA 22-510
2. REVIEW #: 1
3. REVIEW DATE: February 25, 2010
4. REVIEWER: Muthukumar Ramaswamy, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
PIND meeting minutes	Aug. 30, 2004
EOP2 Meeting Minutes	Sep 21, 2005
Safety review IND 69,190 and IND Amendment	Feb. 16, 2007
Pre-NDA meeting Minutes	May 22, 2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 011	02/05/10
Amendment 009	12/03/09
Amendment 008	11/03/09
Amendment 008	11/02/09
Amendment 003	08/25/09
Amendment 002	08/07/09
Original application	08/05/09

7. NAME & ADDRESS OF APPLICANT:

Name: ProStrakan Inc.
Address: 1430 US Highway 206, Suite 110
Bedminster, New Jersey 07921-2652, USA

Executive Summary Section

Representative: Dalena Degrazia MBA

Telephone: 908-234-1096 X228

8. DRUG PRODUCT NAME/CODE/TYPE:

1. Proprietary Name: ABSTRAL®
2. Non-Proprietary Name (USAN): Fentanyl Sublingual Tablets
3. Code Name/# (ONDQA only):
4. Chem. Type/Submission Priority (ONDQA only):
 1. Chem. Type: 3
 2. Submission Priority: S
 - 3.

9. LEGAL BASIS FOR SUBMISSION: This is a 505(b)(2) NDA that relies on FDA's previous findings of safety and effectiveness of the Reference Listed Drug. The Reference Listed Drug for this product is ACTIQ® (fentanyl citrate) Oral Transmucosal Lozenge approved in NDA 20-747.

10. PHARMACOL. CATEGORY: For the management of breakthrough pain in opioid tolerant cancer patients

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 100, 200, 300, 400, 600 and 800 µg

13. ROUTE OF ADMINISTRATION: Sublingual

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

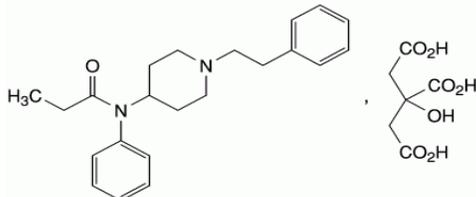
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USP/USAN name: Fentanyl citrate

Chemical names: N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, 2-hydroxy-1,2,3-propanetricarboxylate

Executive Summary Section

Or N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1)
CAS number: 990-73-8

Structure

Molecular formula: C₂₂H₂₈N₂O.C₆H₈O₇

Molecular weight: 528.59 (336.47 as free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
		(b) (4)	Fentanyl citrate	1	Inadequate	01/28/10	Reviewed by Muthukumar Ramaswamy
		(b) (4)	Fentanyl citrate	1	Inadequate	12/14/09	Reviewed by Muthukumar Ramaswamy
		(b) (4)		3	Adequate	01/22/10	Reviewed by Muthukumar Ramaswamy
		(b) (4)		4	Adequate	01/22/10	Reviewed by Muthukumar Ramaswamy

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

Executive Summary Section

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	PAI (b) (4) [REDACTED] is pending	1/21/10	Muthukumar Ramaswamy, Ph.D.
Pharm/Tox	NA		
Biopharm	none		
LNC	Fentanyl Sublingual Tablets	9/29/09	Yana Mille/Rik Lostrito of LNC
Methods Validation	NA		Muthukumar Ramaswamy, Ph.D.
OPDRA	NA		
EA	Acceptable		
Microbiology	NA		

Executive Summary Section

The Chemistry Review for NDA 22-510

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

Approvable pending satisfactory resolution of CMC deficiencies listed at the end and upon acceptable recommendations from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

NA

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Abstral (Fentanyl) sublingual tablet contains (b) (4) fentanyl citrate USP as the active ingredient (b) (4). Fentanyl citrate, also known by its chemical name as N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1) is a μ -opioid agonist and is approximately 80 times more potent than morphine. Fentanyl is a scheduled II controlled drug substance, with an abuse liability similar to other opioid analgesics. It is highly lipophilic, freely soluble in organic solvents and sparingly soluble in water (1:40). (b) (4) fentanyl citrate USP is a white to off-white powder. The drug substance is manufactured (b) (4). The drug substance is packaged in plastic (high density polyethylene) drum container (b) (4). The lots of drug substance manufactured (b) (4) have a retest period (b) (4).

Abstral (fentanyl) sublingual tablet is proposed for the treatment of breakthrough pain in opioid tolerant cancer patients. The sublingual tablets disintegrate rapidly when placed under the tongue. The formulation contains mannitol (b) (4) croscarmellose (b) (4) silicified microcrystalline cellulose (b) (4) and magnesium stearate (b) (4). Compensial grade excipients are used in this formulation. The tablets are available in six different strengths 100 (round), 200 (oval), 300 (triangle), 400 (diamond), 600 (D-shaped), and 800 μ g (capsule) and are readily differentiated by their shape and debossing on one side of the tablets. Tablets are packaged in child-resistant, protective blister cards with peelable foil. Each blister card contains 4 tablets, in pack sizes of 12 (100, 200, 300 and 400 mcg strengths) or 32 (all strengths) tablets. Abstral tablets should be stored at 20-25°C with excursion permitted between 15 and 30°C (59 to 89°C) until ready to use. Abstral should be protected from moisture. The Abstral (fentanyl) singlingual tablets are manufactured at Novartis, Lincoln, NE, USA and Recipharm, Sweden. An expiration period of 36 months for the tablets manufactured at Novartis. Due to limited stability, a 12 month expiration date is recommended for the Abstral tablets manufactured at Recipharm.

Executive Summary Section

B. Description of How the Drug Product is Intended to be Used

The tablets must be placed directly under the tongue immediately after removal from the blister card and allowed to completely dissolve in the sublingual cavity. ABSTRAL tablets should not be chewed, sucked or swallowed. Patients are advised not to eat or drink anything until the tablet is completely dissolved. In patients who have a dry mouth, water may be used to moisten the buccal mucosa **before** taking ABSTRAL.

ABSTRAL is intended to be prescribed only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids, and the manufacturer plans to supply the drug through (b) (4) program. Optimal dose of ABSTRAL will be determined by dose titration in individual patients. An initial dose of ABSTRAL 100 micrograms is recommended, titrating as necessary to control pain through the range of available dosage strengths. Patients should be carefully supervised until an optimal dose is reached for breakthrough pain control. When prescribing Abstral, patients should not be converted on a mcg per mcg basis from another fentanyl product, as this could result in overdose.

The medication guide states that if the breakthrough pain episode is not relieved after 30 minutes, the patients may take only one additional dose using the same strength and must wait at least 2 hours before taking another dose. Following the initial starting dose, patients who need to titrate to a higher dose can be instructed to use 200 microgram tablets or multiples of 100 microgram tablets with their next breakthrough pain episode. Patients should not use more than 4 tablets simultaneously per dose. The efficacy and safety of doses higher than 800 micrograms have not been evaluated in clinical studies in patients.

Once an appropriate dose for pain control has been established, patients should generally use only one ABSTRAL tablet of the appropriate strength per episode of breakthrough pain and should be maintained on this dose. The most common side effects of ABSTRAL are nausea, constipation (not often enough or hard bowel movements), sleepiness and headache.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is approvable pending satisfactory resolution of DMF related deficiencies, CMC deficiencies listed at the end, and upon acceptable recommendations from Office of Compliance on the Firm's readiness to manufacture and test the proposed product.

The NDA 22-510 provides adequate reference to Type II Drug Master files (b) (4) (b) (4) for a description on composition, manufacture, and specification of the drug substance. Resolution of deficiencies pertaining to DMF (b) (4) (b) (4) is pending.

In addition, the NDA contains a common specification for accepting the drug substance at the finished product manufacturing facilities. The specification includes a single sided 3-point specification for particle size distribution (critical quality attribute), and limits for individual and total impurities (critical attribute to assure safety of the drug substance) are part of the drug substance specification. The proposed limits for the specified impurities are as follows (b) (4)

Executive Summary Section

(b) (4)
The limits proposed for impurities are adequate and consistent with ICH Q3A guidelines. The residual solvent impurities and inorganic impurities in the drug substance are controlled in the manufacturing process by appropriate specification that meets USP monograph for fentanyl citrate.

The original manufacturing process was developed at Orexo, Sweden and transferred to Novartis and Recipharm. This NDA contains necessary product development history for optimizing the development of a tablet formulation for sublingual administration. The drug retains the fast onset and individualized dose-titration aspects of Reference Listed Drug (RLD) Actiq®, NDA 20-747. The drug product formulation is a (b) (4) fentanyl citrate, mannitol USP (b) (4), croscarmellose sodium, (b) (4) silicified microcrystalline cellulose, NF (b) (4) and magnesium Stearate (USP/NF,

(b) (4)
The process development, optimization, and scale-up studies were performed using the traditional approach and by Quality by Design (QbD) approach. The QbD studies examined the effect (b) (4) on final drug product characteristics (disintegration, dissolution, content uniformity, bulk and tap density, loss on drying, assay, hardness, and friability). Based on development studies, the firm identified critical unit operations, critical process parameters, in-process controls, and product characteristics for finished product. (b) (4)

Blend uniformity assessment (b) (4) was performed during developmental runs at Novartis, Recipharm and Orexo. Uniformity of the blend was assessed indirectly through content uniformity test by stratified sampling and by uniformity of dosage unit test on finished product (USP <905>) during validation. (b) (4)

The sponsor has also proposed specifications for finished product which include specifications for appearance, identification, assay, degradation products, disintegration time, friability, water content, uniformity of dosage units, and microbiological control. Dissolution and disintegration were used as a tool to monitor product quality during development. (b) (4)

Executive Summary Section

The information pertaining to the composition of the drug product, the specifications for each component, a description of the manufacturing and packaging procedures and in-process controls for the drug product, the specifications necessary to ensure the identity, strength, quality, purity, and potency of the drug product, analytical procedures, and acceptance criteria relating to disintegration, and container closure systems are adequately described.

The acceptance criteria for purity requires that the content of the impurities (b) (4)

These impurity limits were acceptable based on the levels of impurities found in approved fentanyl products, ICH recommendations (ICH Q3B).

The NDA identifies the batches of the drug product used to conduct bioavailability or bioequivalence studies and primary stability studies. The NDA contains master production record, a description of the equipment to be used for the manufacture of a commercial lot of the drug product and a detailed description of the production process for a representative batch of the drug product.

Abstral (100, 200, 300, and 400, and 800µg) tablets used in clinical studies were manufactured at Orexo (100, 200, 300, and 400 µg) and at Novartis (100, 200, 400, and 800 µg strength tablets). Through clinical studies the applicant has established the equivalency of 400 µg strength tablets manufactured at Novartis to batches manufactured at Orexo. The applicant has provided 36 months stability data for 3 batches of all strength tablets manufactured at Novartis to support a 36 month expiration data for the storage of Novartis batches at 25°C.

The batch size (b) (4) the process, and the equipment used at Orexo is the same as Recipharm. The applicant has validated their Abstral tablets manufacturing process used at Recipharm. Test results from process validation demonstrated the suitability of the equipment train and process parameters to provide consistent quality product.

The applicant has provided 36-month stability data for 3 batches of 50 and 400 µg strength tablets and one batch of 100 µg strength tablets manufactured at Orexo. The applicant has provided 3-12 months of stability data (for storage at 25°C/60%RH) for two batches of 50, 300, 800 strength tablets and 18-24 months stability data (for storage at 25°C/60%RH) for one batch of all strength tablets manufactured at Recipharm. The Applicant has also provided 12 month stability data (for storage at 30°C /65%RH) for 1 batch of 100, 200, 300, 400 and 600 mcg strength tablets and 2 batches of 50 and 800mcg tablets manufactured at Recipharm. The applicant has made a commitment to provide periodic stability update on the stability of Recipharm PQ and PV batches as a supplement or through annual report. At this stage, the available stability data does not support a 36 months shelf life claim for batches manufactured at Recipharm. In addition the batches manufactured at Recipharm were never evaluated at any of the clinical studies. A 12 month shelf-life is recommended for Recipharm batches based on data available for 2 batches of 50 and 800 mcg tablets stored at intermediate storage conditions and one batch of all strength tablets stored at 25°C/60%RH for 18-24 months.

Executive Summary Section

Tablets are packaged in child-resistant, protective blister cards with peelable foil. Each blister card contains 4 tablets, in pack sizes of 12 (100, 200, 300 and 400 mcg strengths) or 32 (all strengths) tablets. The primary packaging for Abstral tablets is child resistant ^{(b) (4)} foil/foil aluminum blisters. *The storage recommendation for Abstral tablets is as follows: Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.*

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Muthukumar Ramaswamy /Same date as draft review
Chemistry Team: Leader Prasad Peri
Project Manager Kimberly Compton

C. CC Block

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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/

MUTHUKUMAR RAMASWAMY
02/26/2010
Chemistry review 1

PRASAD PERI
02/26/2010
I concur

DATE: February 10, 2010

TO: NDA 22-510 Inspection Team

FROM: Muthukumar Ramaswamy Ph.D.

THROUGH: Christine Moore, Ph.D

SUBJECT: CMC (Chemistry, Manufacturing & Controls) Considerations for Inspections (PAI) for NDA 22-510 drug product

Fentanyl Citrate is a highly potent drug with narrow therapeutic index. ProStrakan Inc. has submitted a New Drug Application, NDA 22-510 for six different strengths of ABSTRAL[®] (fentanyl) sublingual tablets (100, 200, 300, 400, 600, and 800µg of fentanyl base) for the management of breakthrough pain in opioid tolerant cancer patients. The strength of each fentanyl citrate tablets is expressed in fentanyl base equivalents to meet the labeling convention. This memo provides an overview of drug product manufacturing process, a discussion on Quality by Design (QbD) elements incorporated in drug product (DP) development/manufacturing, and a CMC perspective on areas that require due consideration during the upcoming PAI. *Specific areas of concern are highlighted in italics within the document.*

Manufacturing, Testing, and Release Sites: The original manufacturing process was developed at Orexo, Sweden and transferred to two contract manufacturing sites, Novartis Consumer Health Care, Lincoln, Nebraska and Recipharm AB, Astra, Sweden. (b) (4)

(b) (4)

The drug product manufacturing sites will perform the bulk drug product release and stability testing. The drug products manufactured at Novartis and Recipharm AB, Astra will be packaged at (b) (4) and Recipharm AB, Haninge, Sweden respectively. Prostrakan Inc., NJ will perform the final product release (verification of certificate of analysis) for the Abstral tablets manufactured at Novartis. The proposed batch size for manufacturing Abstral tablets at Recipharm AB and Novartis are (b) (4) respectively.

(b) (4)

(b) (4)

(b) (4)

The sponsor has also proposed specifications for the finished product attributes such as appearance, identification, assay, degradation products, disintegration time, friability, water content, uniformity of dosage units, and microbiological control.

(b) (4)

Blend uniformity assessment (b) (4) was performed during developmental runs at Novartis, Recipharm and Orexo. Uniformity of the blend was assessed indirectly through content uniformity test by stratified sampling and by uniformity of dosage unit test on finished product (USP <905>) during validation at Recipharm.

(b) (4)

In addition, the following comments are considerations with respect to drug product manufacturing:

- 1. Content uniformity is highly critical for this product due to its low dose and narrow therapeutic index. The following are considerations for assuring content uniformity:*
 - a. Firm's procedure for validating the blending mixing process, including sampling location and method*
 - b. Content uniformity testing sampling to be representative of the batch*
 - c. Validation (b) (4)*
 - d. Firm's plans for reevaluating blend and content uniformity on a periodic basis and when making movement within the approved design space*
- 2. The application proposes a design space for expanded flexibility in manufacturing. The following are considerations for the firm's quality system procedures:*
 - a. Firm's plan and procedures for maintaining the design space during product lifecycle*
 - b. Firm's procedures for implementing and documenting changes made to parameters that are within the design space and verifying that product quality is maintained*
 - c. Firm's procedures for evaluation of changes in raw materials (drug substance or excipient) that could affect product quality, including content uniformity*
- 3. Additionally, the following potential GMP issues were identified during the review:*
 - a. Batch record specificity. Tolerance levels (b) (4) are not specified in the batch record provided to the application. Is there an SOP on-site with this information?*
 - b. Firm's procedures for calibrating the (b) (4)*
 - c. Appropriate environmental controls (humidity and temperature) during the drug product processing*
 - d. Validation of hold times (b) (4)s. These should include a measure of content/blend uniformity.*

If you have any questions please feel free to contact Muthu Ramaswamy at 301-796-1676. If possible, the reviewer would like to participate in a pre-approval inspection for the drug product manufacturing site.

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/

DON L HENRY
02/10/2010

MUTHUKUMAR RAMASWAMY
02/11/2010

PRASAD PERI
02/11/2010
I concur

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division: Anesthesia, Analgesia and Rheumatology
NDA: 22-510
Applicant: ProStrakan Inc.
Stamp date: August 5, 2009
PDUFA Date: June 5, 2010
Trademark: Abstral®
Established Name: Fentanyl citrate
Dosage Form: (b) (4) tablets (b) (4) 100, 200, 300, 400,
600 and 800 µg
Route of Administration: Oral
Indication: Management in breakthrough pain in cancer patients
Pharmaceutical Assessment Lead: Danae D. Christodoulou, Ph.D.
YES NO
ONDQA Fileability: √ _____
Comments for 74-Day Letter: √ _____

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock. The referenced approved product is ACTIQ® (fentanyl citrate) Oral Transmucosal Lozenge, NDA 20-747. The application is supported by IND 69,190 and two Drug Master Files for fentanyl citrate.

Abstral® (b) (4) is an alternative formulation to the approved transmucosal fentanyl products, ACTIQ® and FENTORA® for management of breakthrough cancer pain. Fentanyl transmucosal products provide analgesia via rapid onset and individualized dose titration.

The different strengths of Abstral® (b) (4) are differentiated by a unique tablet shape, and by debossing on one side of the tablet. The tablets are packaged in individually sealed child resistant blister packs, which are placed in cardboard cartons. Both blister packs and cartons are color-coded to distinguish between strengths.

B. Review, Comments and Recommendations

Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Chemical names:

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, 2-hydroxy-1,2,3-propanetricarboxylate

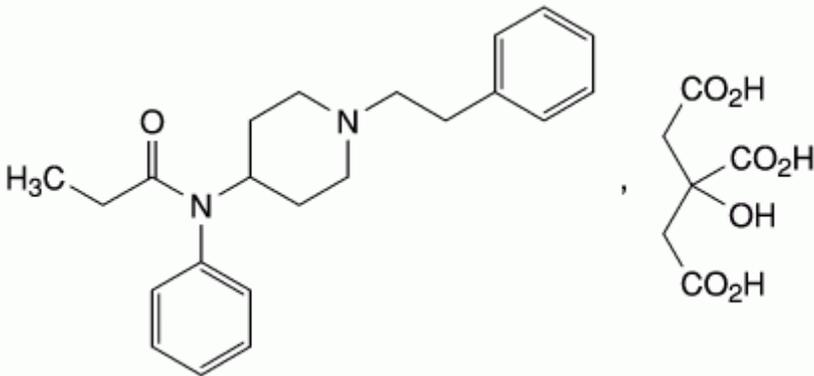
N-(1-Phenethyl-4-piperidyl) propionanilide citrate

Molecular formula: C₂₂H₂₈N₂O · C₆H₈O₇

Molecular Weight: 528.59 g/mol; Free base: 336.47 g/mol

CAS: 990-73-8

Figure 1. Fentanyl Citrate



The drug substance, fentanyl citrate, is supplied by two manufacturers, (b) (4). Description of the manufacturing processes and controls are referenced to the Drug Master Files (b) (4).

(b) (4). Letters of Authorization (LoAs) are included in the NDA, except for the two cross-referenced supporting DMFs. Proposed acceptance specifications by the applicant are included in the NDA. (b) (4).

Characterization:

Details of the drug substance characterization are referenced to the DMFs. The applicant stated that no indication of polymorphism was described in the DMFs from both suppliers. The physical properties of fentanyl citrate, e.g., solubility, morphic form, particle size distribution etc., should be assessed by the primary reviewer, for impact on manufacturability, quality and performance (e.g., disintegration, bioavailability, stability) of the drug product.

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The proposed commercial container closure system is child resistant (b) (4) foil/foil aluminum blisters (b) (4). The proposed, (b) (4) primary packaging material has the same contact material as that used for primary stability batches, (b) (4). Since this is a solid oral dosage form, review of the packaging DMFs is not required, but the firm's acceptance criteria for their packaging materials should be assessed. Letters of Authorization to the packaging DMFs have been included in the NDA.

Stability:

Stability testing of Abstral® tablets is performed under standard ICH conditions at 25°C/60% RH, and 40°C/75% RH. Stability protocols and post-approval stability commitment are provided in the NDA. Long term stability data up to 36 months on three production scale batches of each strength are included (Novartis). The Recipharm batches longest stability data are up to 24 months. The proposed expiration dating is 36 months based on real time stability data.

Labeling

Labeling information of the container labels and packaging insert should be assessed with respect to CMC related information. SPL labeling has not been included and should be requested from the applicant.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMFs (b) (4) should be assessed. DMF (b) (4) has not been reviewed before.
2. The physical properties of fentanyl citrate, e.g., solubility, morphic form, particle size distribution etc., should be assessed for impact on manufacturability, quality and performance (e.g., disintegration, bioavailability, stability) of the drug product.
3. The proposed specification (b) (4) and its mutagenic potential should be assessed in consultation with the Toxicology division. In addition, the need of specification for (b) (4) should be assessed.
4. Limits if impurities and related substances in the drug substance as per ICH Q3A(R), in consultation with the Toxicology Division. Note that the proposed specification (b) (4) exceeds the ICH limit.
5. Method Validation: HPLC methods used for determination of specified impurities and assay at Recipharm and Novartis and their comparability.
6. Proposed retest date (b) (4).
7. The adequacy of the two API manufacturing processes, comparability of API produced by the two processes and alternate sites and ultimately comparability of the resulting drug product should be assessed.
8. The suitability of the compendial specifications of excipients for drug product manufacturability, quality and performance should be assessed.
9. The comparisons and equivalency of the drug product manufacturing processes and sites should be assessed.
10. Critical parameters identified during manufacturing process development (e.g., homogeneity, blend uniformity), in-process controls and holding times of any intermediates.
11. The proposed fentanyl citrate (b) (4) should be assessed.
12. The Quality by Design studies for drug product critical manufacturability attributes and the process development should be assessed in consultation with a Manufacturing Sciences reviewer.
13. Drug product specifications, e.g., dissolution, impurity/degradant limits as per ICH Q3B(R), in consultation with the Toxicology Division.
14. Proposed Abstral® tablets expiration dating of 36 months. The expiry date was proposed based on 36-month real time data and comparability of the (b) (4) (primary) versus (b) (4) (proposed commercial) blisters.

D. Comments for 74-day Letter:

- Provide labeling in Structured Product Labeling (SPL) format.

E. **Recommendation for fileability:** The NDA is fileable based on sufficient number of NDA batches, and long term stability data for the drug substance and product. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is recommended for team review. A substantial amount of process development was performed using Quality by Design (QbD) principles. A consultation from the manufacturing sciences group for evaluation of all QbD studies in the NDA, should be requested.

Consults:

1. Toxicology

2. Manufacturing Sciences, ONDQA

The primary reviewer, in conjunction with the project manager, should initiate the above consults.

Danae D. Christodoulou, Ph.D.
Pharmaceutical Assessment Lead

10/09/2009
Date

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA

10/09/2009
Date

NDA Number: 22-510

Supplement Number and Type:

Established/Proper Name:

Fentanyl Citrate ^{(b) (4)}/Abstral®

Applicant: ProStrakan

Letter Date: 08/05/09

Stamp Date: 08/05/09

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Clarifications and communications with OC.
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		X	Clarifications and communications with OC.

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF(s) [REDACTED] (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF(s) [REDACTED] (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF(s) [REDACTED] (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF(s) [REDACTED] (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solid Oral Dosage Form)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
		(b) (4)	Fentanyl		(b) (4)
			Fentanyl Citrate		API
			Fentanyl Citrate		API (b) (4)
			Fentanyl Citrate		(b) (4)

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			Based on pre-NDA agreements and substantial body of data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Name of

PAL: Danae Christodoulou 9/16/09
 Division of Pre-Marketing Assessment I
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief: Ali Al-Hakim
 Division of Pre-Marketing Assessment I
 Office of New Drug Quality Assessment

Date

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

/s/

DANAE D CHRISTODOULOU
10/09/2009
Initial Quality Assessment

ALI H AL HAKIM
10/11/2009