NDA 22-266

ONSOLIS (fentanyl buccal soluble film)

Biodelivery Sciences International, Inc.

Xavier Ysern, PhD
ONDQ/ DPA I/ Branch II

Clinical Review Division: DAARP

CHEMISTRY REVIEW

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-266

2. REVIEW #: 2

3. REVIEW DATE: 31-Jul-2008

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
--	--

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission:	31-Oct-2007
Amendment(s):	08-Jul-2008 (revised dissolution and impurity DP specifications)

7. NAME & ADDRESS OF APPLICANT:

Name:	BioDelivery Sciences international
Address:	2501 Aerial Center Parkway Suite 205 Morrisville, NC 27560
Representative:	David T. Wright, PhD, RAC Director of Regulatory Affairs
Telephone:	(919) 653-5168

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Onsolis (accepted as tradename),
BEMA™ Fentanyl (originally proposed by applicant)

b) Non-Proprietary Name (USAN): Fentanyl buccal soluble film (assigned by LNC)

c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
[Reference Drug Product: Actiq (fentanyl citrate) oral transmucose lozenge. Holder of approved application: Cephalon]

10. PHARMACOL. CATEGORY: Analgesic, narcotic (opiate)

11. DOSAGE FORM: Film

12. STRENGTH/POTENCY: 200-, 400-, 600-, 800-, and 1200-µg

13. ROUTE OF ADMINISTRATION: Buccal Transmucose

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view the application is recommended for approval. Based on the submitted stability data, an expiry of 24 months is granted under the recommended **storage conditions: "Store at [redacted] excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]."** b(4)

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Introduction

Fentanyl is a potent, short acting, synthetic opioid analgesic used in anesthesia, post-operative analgesia, and chronic pain management. Fentanyl acts as a selective μ-opioid receptor agonist with potency approximately 80-fold **greater than that of morphine. Fentanyl was first discovered in the late 1950's by Dr. Paul Janssen and was later** introduced as an analgesic into medical practice in the 1960s. The analgesic activity of fentanyl is well known and fentanyl has been marketed as an analgesic agent in several different dosage forms (e.g. intravenous or intramuscular administration, transdermal patch, lollipop or lozenge for oral transmucosal delivery). Due to its high potential for abuse, which may lead to severe psychological or physical dependence, fentanyl is listed as a Schedule II drug under the Controlled Substances Act for the United States. In this NDA, NDA 22-266, Biodelivery Sciences International proposes a new dosage form for fentanyl, Onsolis (fentanyl buccal soluble film), where fentanyl is delivered through the buccal **mucosa. Actiq (fentanyl citrate) oral transmucose lozenge (Cephalon's NDA 20-747) is the reference drug product** (comparator). Onsolis, the subject of this NDA, has better bioavailability than Actiq.

- Drug Substance

The drug substance is the citrate salt of the active component fentanyl. Fentanyl citrate, a well characterized **compound, is supplied and manufactured by [redacted] hemistry, Manufacture and Controls' (CMC) information is referred to [redacted] proprietary Type [redacted] Drug Master File (DMF [redacted]**. Fentanyl citrate is an off-white powder. Fentanyl is a weak base with pK_a values of 7.3 and 8.4. Its solubility is approximately 25 mg/mL in water at room temperature. b(4)

Potential impurities and degradation products in [redacted], **fentanyl citrate drug substance include** [redacted] b(4)

[redacted] The final [redacted] of fentanyl citrate is [redacted] No residual solvents, other than [redacted], are detected. [redacted] b(4)

The specifications for fentanyl citrate drug substance that will be used by the drug product manufacturer, Aveva Drug Delivery Systems (Aveva), comprise Appearance (visual), Identification (IR and UV spectroscopy), Loss on Drying (USP <731>), Residue on Ignition (USP <281>), Heavy Metals (USP <231>), Ordinary Impurities (TLC), Assay (titration and HPLC), and Purity and Related Substances (HPLC). The content of fentanyl citrate, calculated on dry **basis, is 98.0–102.0 %. The acceptance criteria for Related Substances such as the** [redacted] is NMT [redacted] for each of them, and NMT [redacted] for [redacted]. The content of Unknown Related Substances (each) is [redacted] and the total content of Related **Substances does not exceed [redacted]; fentanyl specifications meet USP fentanyl citrate monograph.** b(4)

container closure systems for the fentanyl citrate drug substance can be used for packaging. b(4)

Supported by stability studies, a retest date has been set for fentanyl citrate drug substance. b(4)

- Drug product

The drug product ONSOLIS, fentanyl buccal soluble film, is a flat bilayer rectangle with round corners, pink on one side and white on the other side. The pink mucoadhesive layer contains the drug substance, fentanyl citrate, and the white backing layer controls the erosion rate and residence time of the dosage form in the mouth. The white backing layer does not contain drug product, and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The drug product is designed to provide drug release through the buccal mucosa when the pink side is placed on the inside of the cheek. The composition of the drug substance within the mucoadhesive layer is the same for all product strengths. The drug product units are designed to erode over a period of approximately 30 minutes. The product design results in delivery of approximately 70 % of the dose through the buccal mucosa and 30 % of the dose is swallowed (study FEN-114). Bioavailabilities of oral and ONSOLIS fentanyl are 35 % and 71 %, respectively.

The drug product is available in five strengths: 200, 400, 600, 800, and 1200 mcg (µg) fentalyl free base per unit. Fentanyl citrate, the drug substance, is contained in the mucoadhesive layer. The excipients sodium benzoate (), methylparaben propylparaben b(4)
citric acid vitamin E hydroxypropyl cellulose , hydroxyethyl cellulose and water are found in both mucoadhesive and backing layers (common excipients). Besides the common excipients, the mucoadhesive layer contains propylene glycol , ferric oxide monobasic sodium phosphate sodium hydroxide , tribasic sodium phosphate polycarbophil and carboxymethylcellulose b(4)
In addition to the common excipients, the backing layer has titanium dioxide , saccharin sodium and peppermint oil . All excipients meet compendial requirements.

The commercial formulation is the same as that used in the Phase 3 clinical trials. The Phase 3 clinical formulation had the same excipients as the formulations used in the Phase 1 clinical trials, at the same concentrations, except the pH was adjusted to different values. The formulation used in the pivotal nonclinical study was the same as the Phase 1 formulation.

The drug product is manufactured mainly by

b(4)

The units are packaged by in preprinted pouches, and the pouches are boxed.

The thickness of the film product is fixed by design (mucoadhesive and backing layer thickness are b(4)
, respectively), so the fentanyl dose is defined by size and defined by the surface area. Five strengths are proposed for commercialization, their film sizes are:

- 200 µg *(thickness x length x width)*
- 400 µg
- 600 µg b(4)
- 800 µg
- 1200 µg

Drug product specifications include appearance (visual), identification (RP HPLC and UV-Vis spectroscopy), assay (RP HPLC), Purity (HPLC), content uniformity (RP HPLC), unit weight (gravimetry), pH (potentiometry), Dissolution (RP HPLC), water content (Karl Fischer titration), microbial limits (USP <61>), and pouch integrity (expansion under pressure reduction in a vacuum enclosure). The acceptance criteria for purity requires that the content of the impurities and not to b(4)
exceed , and (w/w) respectively, any unknown impurity no more than and the total impurity

content should be lower than —— (w/w). These impurity limits were acceptable based on the levels of impurities found in approved fentanyl products, ICH recommendations (ICH Q3B(r)), and the results of toxicology studies. Although the product is neither a tablet nor a capsule, dissolution testing is performed using USP apparatus 1 (25 mM Phosphate buffered medium, pH 6.4, 60-100 mL, 37 ± 0.5 °C, 100 rpm) as a quality control (Q —— at 30 minutes). Since the formulation is immediate release dosage form, an *in vivo in vitro* correlation has not been performed. Also, the environment where the product erodes (oral surface) is different from the dissolution testing medium. All the proposed validated analytical methods fulfill their intended purpose. b(4) b(4)

Each individual unit is sealed in a multilayer —— including foil. The package material is a —— multilayer —— The product contact layer is —— approved for food contact under 21 CFR Part 177-Indirect Food Additives: Polymers Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces. The —— b(4) b(4)

Labeling is printed directly on the paper. The different strengths have different colored packages. They are child-resistant and have a slit to aid in tearing open, or the package may be cut open with scissors. They are packaged into a cardboard carton.

Stability data is provided for 26 lots. Twenty-two represent the commercial formulation and four lots were formulated at different pHs. Based on statistical analysis extrapolation, the applicant requested a — expiry date for the drug product. Judged by the available data, 18 months at the storage condition (undergoing study) and 6 months under accelerated condition (completed study) from 18 lots, a 24-month expiry dating is granted by the Agency. b(4)

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

The drug product is indicated for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The drug product is designed to provide drug release through the buccal mucosa (inner lining of cheek) when the mucoadhesive layer of the film side (pink side) is placed on the inside of the cheek.

Dose and frequency is prescribed by the physician. In order to use the drug product, the drug product film is removed from the foil package (pouch) according to the tearing instructions. The drug product should be placed on a dry finger, with the pink side facing up, and carefully placed inside the mouth with the pink side against the inside of the moistened cheek. The film should be press with the finger against the cheek holding for 5 seconds after that remove the finger from the film which will stick to the inside of the cheek. The dose unit is left in place until it dissolves, usually within 15 to 30 minutes after application.

C. Basis for Approvability or Not-Approval Recommendation

Adequate CMC information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP) manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments. All pending issues have been resolved satisfactorily; the manufacturing facilities have been found acceptable (District Office recommendation dated July 30, 2008).

III. Administrative

A. Reviewer's Signature	Xavier Ysern, PhD	Review Chemist/ ONDQA/ DPA I/ Branch II
B. Endorsement Block	Ali Al-Hakim, PhD	Branch Chief/ ONDQA/ DPA I/ Branch II
C. CC Block	Kimberly Compton	Project Manager/ OND/ ODE II/ DAARP

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

□(s0P□&k4S□&17.27c66F 31-JUL-2008 FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22266/000	Action Goal:	
Stamp:	31-OCT-2007	District Goal:	02-JUL-2008
Regulatory Due:	31-AUG-2008	Brand Name:	FENTANYL CITRATE / BEMA
Applicant:	BIODELIVERY SCI 801 CORPORATE CENTER DR STE 210 RALEIGH, NC 27607	Estab. Name: Generic Name:	FENTANYL FENTANYL CITRATE
Priority: 3S		Dosage Form:	(TROCHE)
Org Code: 170		Strength:	200-1200 MCG

Application Comment: AVEVA PERFORMS ' [redacted] b(4)

(on 14-NOV-2007 by X. YSERN () 301-796-2410)
THE DRUG PRODUCT BEMA FENTANYL, BIOERODABLE MUCOADHESIVE SYSTEM IS A FLAT BILAYER RECTANGLE [redacted] S THE MUCOADHESIVE LAYER THAT [redacted] THE WHITE LAYER [redacted] b(4)

[redacted] THE UNIT IS DESIGNED TO ERODE OVER A PERIOD OF APPROXIMATELY 30 MINUTES (on 15-APR-2008 by X. YSERN () 301-796-2410)

FDA Contacts:	X. YSERN	301-796-2410 , Review Chemist
	D. CHRISTODOULOU	301-796-1342 , Team Leader

Overall Recommendation: ----------

Establishment: CFN [redacted] FEI [redacted] b(4)
AVEVA DRUG DELIVERY SYSTEMS INC
3250 COMMERCE PKY
MIRAMAR, FL 33025

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: NEC OAI Status: NONE

Estab. Comment: AVEVA PERFORMS [redacted] b(4)

(on 14-NOV-2007 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-NOV-2007				YSERNX
SUBMITTED TO DO	15-NOV-2007	GMP			KIEL
INSPECTION SCHEDULED	28-NOV-2007		26-MAY-2008		STURCOVS
INSPECTION PERFORMED	18-JUL-2008		18-JUL-2008		STURCOVS
EI WILL BE CLASSED "VAI"; DEFICIENCIES IN [redacted] OBSERVED; DO RECOMMENDATION	30-JUL-2008			ACCEPTABLE INSPECTION	STURCOVS

b(4)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

EI WILL BE CLASSED "VAI" [redacted] DEFICIENCIES WERE OBSERVED. b(4)

Establishment: CFN [redacted] FEI [redacted] b(4)

DMF No: [redacted] AADA:
Responsibilities: [redacted] b(4)

Profile: CSN OAI Status: NONE

Estab. Comment: [redacted]

(on 14-NOV-2007 by X. YSERN () 301-796-2410) b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-NOV-2007				YSERNX
OC RECOMMENDATION	15-NOV-2007			ACCEPTABLE BASED ON PROFILE	KIEL

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

/s/

Xavier Ysern
7/31/2008 09:17:58 AM
CHEMIST

Ali Al-Hakim
7/31/2008 11:56:36 AM
CHEMIST