



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

Date: July 17, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Claudia Karwoski, Pharm.D., Acting Director
Division of Risk Management (DRISK)

From: Scientific Lead: Jeanine Best, MSN, RN, PNP, Senior Drug Risk
Management Analyst, DRISK
Team Members:
Suzanne Berkman, Acting Team Leader, DRISK
Mary Dempsey, Risk Management Program Coordinator, DRISK

Subject: Deferral Memo for Proposed RiskMAP

Drug Name: Onsolis (fentanyl bioerodible mucoadhesive) _____ **b(4)**

Submission Number: NDA 22-266

Applicant/sponsor: BioDelivery Sciences International Inc.

OSE RCM #: 2007-2577

1 INTRODUCTION

This memorandum follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Onsolis (fentanyl bioerodible mucoadhesive _____), Risk Minimization Action Plan (RiskMAP) submitted to FDA by BioDelivery Sciences International, Inc. on October 31, 2007, as part of the original New Drug Application (NDA) 22-266. b(4)

Onsolis, a potent opioid analgesic (Schedule II), is an oral transmucosal system for delivery of fentanyl across the buccal mucosa, and was submitted 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.¹ Onsolis comes as a flexible, flat, bi-layer film; the mucoadhesive layer of the film contains fentanyl citrate and adheres to moist buccal mucosa upon contact. The backing layer of the film is used to minimize the fentanyl release into the oral cavity in order to maximize fentanyl transmucosal diffusion. Onsolis has five proposed dosage strengths: 200, 400, 600, 800, and 1200 micrograms.

2 MATERIAL REVIEWED

- Draft Onsolis (fentanyl bioerodible mucoadhesive _____), Risk Minimization Action Plan (RiskMAP), October 31, 2007
 - Best J. Fentora Advisory Committee Background Package: OSE Review; Fentora Risk Minimization Action Plan (RiskMAP) and Postmarketing Experience, April 8, 2008
 - Transcript of the Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, May 6, 2008
- b(4)

3 SPONSOR'S RISK MANAGEMENT PROPOSAL

The Sponsor identified the following risks, 1) use in opioid non-tolerant patients; 2) misuse; and, 3) unintended (accidental) exposure, and proposed the risk management plan that includes:

1. Labeling
 - Package Insert,
 - Medication Guide
 - Carton label/checklist
2. Education
 - Labeling
 - Independent CME
3. Surveillance
 - Spontaneous reporting
 - Expedited reporting
 - Active surveillance and monitoring of abuse, misuse, and diversion
4. Evaluation
 - Periodic analysis of surveillance and monitoring activities for abuse, misuse, and diversion
 - Physician, pharmacist, and patient surveys to evaluate knowledge, attitudes and behavior from education efforts
 - Assess use in non-opioid tolerant patients using patient longitudinal drug use data

¹ See Cover Letter for NDA 22-266 submitted October 31, 2007

4 DISCUSSION

Onsolis is similar to the two other currently marketed oral transmucosal fentanyl products (e.g., Actiq and Fentora); and therefore, the potential safety concerns are the same, and the anticipated adverse events are expected to be similar. The identified risks and proposed RiskMAP for Onsolis is consistent with the current risk management measures for Actiq and Fentora. However, these measures have been determined to be inadequate based on the joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory committees convened on May 6, 2008 to discuss Fentora.²

Additional risk mitigation strategies are necessary for all oral transmucosal fentanyl products, including Onsolis, in order to attain a favorable benefit/risk balance. Postmarketing data for Actiq and Fentora indicate increasing use in opioid non-tolerant patients, abuse, misuse, and diversion, and unintended (accidental) use, with all data trending in a negative direction. Misuse and medication errors (including conversion errors) account for the majority of the adverse event reports in the Adverse Event Reporting System (AERS).³ The concerning postmarketing data-trending and medication errors leads us to believe that current risk mitigation measures for Actiq and Fentora are not effectively mitigating the identified risks; and therefore, these measures will not effectively mitigate the identical risks identified for Onsolis.

In addition, Actiq and Fentora, and now also Onsolis differ in their bioavailability; and therefore, are not equivalent on a mcg per mcg basis, but all three products have overlapping dosage strengths. Thus, the addition of Onsolis to the market creates additional opportunity for the medication errors (including conversion errors) noted above.

Requests for comprehensive Risk Evaluation and Mitigation Strategy (REMS) to mitigate the potential serious risks (use in opioid-non-tolerant individuals, misuse, and unintended or accidental exposure) associated with the oral transmucosal fentanyl products will be sent to the affected Sponsors. The requested REMS will include a Medication Guide, a Communication Plan, Elements to Assure Safe Use, an Implementation System, and a Timetable for Assessments.

5 CONCLUSIONS

OSE defers comment on proposed risk management measures for Onsolis until submission of a REMS comparable to what is being requested for the marketed oral transmucosal fentanyl products which will include a Medication Guide, a Communication Plan, Elements to Assure Safe Use, an Implementation System, and a Timetable for Assessments is submitted. The Onsolis proposed REMS should be submitted as part of the Sponsor's response to the "Complete Response" action taken by DAARP for this review cycle.

² Transcript of the Joint Meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, May 6, 2008

³ Best J. Fentora Advisory Committee Background Package: OSE Review; Fentora Risk Minimization Action Plan (RiskMAP) and Postmarketing Experience, April 8, 2008

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this page is the manifestation of the electronic signature.**

/s/

Mary Dempsey
7/17/2008 10:21:00 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
7/17/2008 11:22:20 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: May 29, 2008

TO: Kimberly Compton, Regulatory Project Manager
Ellen Fields, M.D., Medical Officer

FROM: Sherbet Samuels, R.N., M. P. H.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-266

APPLICANT: BioDelivery Sciences International, Inc. (BDSI)

DRUG: BEMA Fentanyl (Fentanyl BioErodable Mucoadhesive **b(4)**)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

CONSULTATION REQUEST DATE: December 19, 2007

DIVISION ACTION GOAL DATE: August 29, 2008

PDUFA DATE: August 29, 2008

I. BACKGROUND:

The sponsor, BDSI has submitted a new drug application (NDA 22-266) for marketing approval of BEMA™ fentanyl 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. Dr. Rohit Kapoor and Dr. James North were selected for inspection due to enrollment of large number of subjects in the two pivotal studies for this NDA. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects’ rights, safety, and welfare.

The protocols inspected include:

- Protocol FEN-201 entitled “A double-blind, placebo controlled evaluation of the efficacy, safety and tolerability of BEMA™ fentanyl in the treatment of breakthrough pain in cancer subjects”
- Protocol FEN-202 entitled “An open label, long-term treatment evaluation of the safety of BEMA™ fentanyl use for breakthrough pain in cancer subjects on chronic opioid therapy”

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Protocol #:	Inspection Date	Final Classification
James North, M.D. Center for Clinical Research 145 Kimel Park Drive Winston Salem, NC 27103	Protocols FEN201 & FEN202	February 11-March 6, 2008	NAI
Rohit Kapoor, M.D. 12602 Toepperwein, Suite 202 San Antonio, TX 78233	Protocols FEN201 & FEN202	April 1-10, 2008	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. James North, M.D.
Center for Clinical Research
145 Kimel Park Drive
Winston Salem, NC 27103

- a. **What was inspected:** The inspection included a review of source documents and comparison with data listings. Regarding protocol FEN 201, 16 subjects were enrolled and 9 subjects completed the study. An audit of 9 subjects’ records was conducted. Regarding protocol FEN 202, 13 subjects were enrolled

and 6 subjects completed the study. An audit of 6 subjects' records was conducted.

- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data from this site appear acceptable.

2. Rohit Kapoor, M.D.
12602 Toepperwein, Suite 202
San Antonio, TX 78233

- a. **What was inspected:** The inspection included a review of source documents and comparison with data listings. Regarding protocol FEN 201, 27 subjects were enrolled. An audit of 11 subjects' records was conducted. Regarding protocol FEN 202, 27 subjects were enrolled. An audit of 8 subjects' records was conducted.
- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data from this site appear acceptable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above inspection of Dr. Kapoor and Dr. North found no significant regulatory violations. Data from these sites appear acceptable in support of the pending application.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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

/s/

Sherbert Samuels
6/2/2008 07:23:51 AM
CSO

Constance Lewin
6/3/2008 01:24:26 PM
MEDICAL OFFICER

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, April 10, 2008 6:25 PM
To: 'David T. Wright'
Cc: Compton, Kimberly
Subject: CMC and one additional labeling request for N 22-266 BEMA

Hi Dave,

I hope things are going well.

I have the following request from our CMC reviewer for BEMA

Your proposed acceptance criterion, $Q = \text{---} \text{---} \text{---}$ minutes, is rather permissive and it is not fully supported by the development and stability data. A Q value defined at an earlier time, e.g., 30 minutes, would be more discriminatory as a quality control test. Therefore, provide:

b(4)

- A revised dissolution specification and its justification.
- Dissolution profile data from stability lots.

And the following additional labeling request from the clinical team in addition to the labeling items in our recent letter:

In reference to Section 6 of your proposed package insert (PI), Tables 1 and 2 and other listings of adverse events should be based on all treatment emergent adverse events reported in the ISS, not just the adverse drug reactions (related to opioids) as listed in the draft label. Please revise your PI accordingly.

Please let me know if you have any questions on these requests.

Thanks,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191