CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-266

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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 16, 2009
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) Office of New Drugs (OND)
Thru:	Claudia Karwoski, PharmD, Acting Director Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	**Scientific Lead:** Jeanne Perla PhD., Risk Management Analyst
Subject:	Update to Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	ONSOLIS™ (fentanyl buccal soluble film)
Application Type/Number:	NDA 22-266
Applicant/sponsor:	Bio Delivery Sciences International, Inc.
OSE RCM #:	2008-1994

This memo is to provide an update to the review of the Risk Evaluation and Mitigation Strategy review dated June 22, 2009. The final approved REMS has one change – the education and enrollment of distributors has been moved to the implementation system.

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/s/

Mary Dempsey
7/16/2009 07:43:03 AM
DRUG SAFETY OFFICE REVIEWER

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For Claudia Karwoski

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
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Date:	June 22, 2009
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) Office of New Drugs (OND)
Thru:	Claudia Karwoski, PharmD, Acting Director Division of Risk Management (DRISK) Office of Surveillance and Epidemiology (OSE)
From:	**Scientific Lead:** Jeanne Perla PhD., Risk Management Analyst **Team Members:** **DRISK** Marcia Britt, PhD, Regulatory Health Specialist Mary Dempsey, Risk Management Program Coordinator Jodi Duckhorn, MA Social Scientist, Patient Labeling and Education TL Brian Gordon, MA, Social Science Reviewer Sharon Mills, BSN, RN, CCRP, Patient Product Information Reviewer Mary Willy PhD, Senior Risk Management Analyst **Division of Pharmacovigilance II** Afrouz Nayernama, PharmD, Safety Evaluator **Division of Medication Error Prevention and Analysis** Kristina Arnwine, PharmD **Division of Drug Marketing, Advertising and Communication** Mathilda Fienkeng, PharmD, Regulatory Review Officer Twyla Thompson, PharmD, Regulatory Review Officer **Office of Compliance Division of Risk Management and Surveillance** Agnes Plante BSN, RN Consumer Safety Officer Suzanne Barone Ph.D. Team Leader for Risk Management and Strategic Problem Solving
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	**ONSOLIS™ (fentanyl buccal soluble film)**
Application Type/Number:	NDA 22-266
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EXECUTIVE SUMMARY

Onsolis (fentanyl buccal soluble film) is an opioid analgesic proposed 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. In response to an August 25, 2008 Complete Response(CR) letter, the Sponsor submitted a Risk Evaluation and Mitigation Strategy (REMS) to address the risk of overdose, abuse, addiction and serious complications due to medication errors. The REMS includes a Medication Guide, Communication Plan, Elements to Assure Safe Use (certification of prescriber, pharmacy, and patient), an Implementation System, and a Timetable for Submission of Assessments. After multiple submissions to address the Agency's concerns, agreement was reached within the Agency and with the Sponsor on all of the components of the REMS including the REMS document, the education tools to be used within the REMS, the implementation plan, the frequency of reporting to the Agency, and the REMS assessment plan.

1 BACKGROUND

1.1. INTRODUCTION

Onsolis (fentanyl buccal soluble film) is designed to provide drug release through the buccal mucosa when the film is placed on the inside of the cheek. Onsolis is available in five strengths: 200, 400, 600, 800, and 1200 mcg (μg) of fentanyl. The proposed indication is for the management of breakthrough pain in cancer patients, 18 years or older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

The clinical review of the clinical trials did not identify any unexpected adverse events, but did find the typical opioid-related adverse events. In addition to the potential risk of abuse, misuse, and addiction, one major concern is the potential for medication errors. With the introduction of Onsolis, there will be three oral transmucosal fentanyl (OTF) products available on the market (Fentora, approved in 2006; Actiq, approved in 1998). All three have differences in bioavailability and all three have overlapping dosage unit strengths. Because the three products differ in bioavailability, they are not interchangeable on a microgram by microgram basis (ref medical officer). Post marketing cases of medication errors have been reported with the currently approved OTF products.

The other concern is potential use of Onsolis in non-opioid tolerant patients. Individuals using Onsolis who are not tolerant to opioids are at risk for clinically significant and life-threatening respiratory depression. Within the first year of the approval of Fentora, the Agency received reports of serious adverse events and death from use of Fentora in non-opioid tolerant patients.

Previous risk management programs for Actiq and Fentora have failed to adequately address the above concerns. Based on the new safety information, the Agency determined that a REMS was necessary for the all OTF products to ensure the benefits of the drug

outweigh the risks. The Sponsor was notified of the requirement for a REMS in the August 25, 2008 CR letter.

1.2. REGULATORY HISTORY

BioDelivery submitted Onsolis for review October 31, 2007 which included the Onsolis Risk Minimization Action Plan (RiskMAP). On February 11, 2008 an email requesting additional information was sent to the sponsor. The RiskMAP was amended February 22, March 25, April 16, and May 7, 2008.

On August 25, 2008 the Sponsor was sent a Complete Response letter and advised that a REMS was necessary for Onsolis to ensure the benefits of the drug outweigh the risks of overdose, abuse, addiction and serious complications due to medication errors. BioDelivery submitted a Meeting Briefing Package October 23, 2008 for the scheduled end of review meeting November 17, 2008. Based on the feedback at the November 17, 2008 review meeting, BioDelivery submitted a proposed REMS and supporting documents on December 12, 2008. Subsequent revised REMS were submitted February 27, March 16, April 14, May 15, and June 12, 2009.

2. MATERIALS REVIEWED

2.1. DATA AND INFORMATION SOURCES

1) Onsolis Risk Minimization Action Plan, submitted October 31, 2007
2) Clinical Review, Ellen Fields, M.D., June 6, 2008
3) Complete Response Letter, Onsolis (NDA 22-266), August 25, 2008
4) Onsolis Meeting Briefing Package including a REMS proposal and questions submitted October 20, 2008
5) Meeting minutes for end of review meeting which was held November 17, 2008
6) Proposed REMS submitted December 12, 2008.
7) Revised REMS proposal submitted February 27, 2009
8) Revised REMS proposal submitted March 16, 2009
9) Revised REMS proposal submitted April 14, 2009
10) Revised REMS proposal submitted May 15, 2009
11) Revised REMS proposal submitted June 12, 2009

2.2. ANALYSIS TECHNIQUES

The submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and responsiveness to comments submitted to the Sponsor as part of the ongoing review.

3. PROPOSED REMS

The Sponsor's proposed REMS, FOCUS (Full Ongoing Commitment to User Safety) includes the following agreed upon components:

3.1. GOALS

The goal of the FOCUS Program is to mitigate the risk of fentanyl overdose, abuse, addiction, and serious complications due to medications errors by:

1. Helping to assure proper patient selection, including avoidance of the use of Onsolis in opioid non-tolerant patients;
2. Reducing the risk of exposure to Onsolis in persons for whom it was not prescribed, including accidental exposure in children; and
3. Training prescribers, pharmacists, and patients about proper dosing and administration.

3.2. REMS ELEMENTS

3.2.1. Medication Guide

The healthcare provider who prescribes Onsolis will provide a copy of the Medication Guide to the patient at the time of patient enrollment. Additionally, a Medication Guide will be dispensed with each Onsolis prescription, by the certified and enrolled specialty pharmacy distributor.

3.2.2. Communication Plan

The Communication Plan for healthcare providers includes the following materials:

1. For Prescribers: Dear Prescriber Letter (provided at product launch),

   The Sponsor will provide education to a group of targeted prescribers who prescribe —— of the total prescriptions for oral transmucosal fentanyl products to include predominately pains management specialists, anesthesiologists, physical medicine and rehabilitation physicians, oncologists, oncology nurse practitioners, and general practitioners.

2. ——————————————————————— b(4)

3.2.3. Elements to Assure Safe Use

1. Healthcare providers who prescribe Onsolis are educated and enrolled in the program

   Prescribers review educational material and complete a prescriber enrollment form (including a Prescriber Knowledge Assessment). The enrollment form includes an agreement to comply with program requirements including ensuring that the patient is opioid tolerant, enrolling and counseling patients, and attesting that they understand that Onsolis is not bioequivalent with any other oral transmucosal fentanyl citrate products. Prescribers will be reenrolled every 2 years.

2. Each patient treated with Onsolis will be counseled and enrolled in the program for documentation of safe use conditions

Patients are counseled by their prescriber and complete a patient enrollment form. The patient enrollment form includes a section where the prescribers acknowledge that the patient is opioid tolerant and that they reviewed the Medication Guide with the patient. The patient acknowledgements include that they received a Medication Guide, that they will not share Onsolis with others, and that they will store the drug away from children. Patients are reenrolled every 2 years.

3. [redacted] b(4

4. Education and enrollment of specialty pharmacies that dispense Onsolis.

   Pharmacists-in-charge review educational material and complete a pharmacy enrollment form. The enrollment form includes an agreement to make sure that all pharmacy staff are trained on the FOCUS program, ensure that pharmacy staff only dispense Onsolis after confirming that patients have met safe use conditions (patients are enrolled and prescription from an active prescriber; patient is opioid tolerant) and that they understand that Onsolis is not bioequivalent with any other oral transmucosal fentanyl citrate products. They further agree to dispense the Medication Guide with each prescription. Pharmacies are reenrolled every 2 years.

3.2.4. IMPLEMENTATION SYSTEM

1. Maintain a database of enrolled entities
2. Monitor the distribution of Onsolis
3. Monitor the dispensing of Onsolis by active FOCUS pharmacies.
4. Monitor, audit, and evaluate all active FOCUS pharmacies, distributors, and the FOCUS Program.
5. Monitor and evaluate the elements to assure safe use in the manner described in the REMS Supporting Document, and take reasonable steps to work to improve implementation of these elements.

3.2.5. TIMETABLE FOR SUBMISSION OF ASSESSMENT

The Sponsor will submit a REMS Assessment at 6 months and 1 year after approval of the NDA for Onsolis and annually thereafter. Assessments are submitted to FDA within 60 days after the close of the respective assessment interval. The REMS assessment plan will be included in the Approval Letter.

The REMS Assessment Plan (information for assessment for the REMS assessment) was summarized in the REMS Supporting Document. Briefly, it will include the following:

1. Data (during the reporting period and cumulative) from the Prescriber and pharmacy education and enrollment report from the FOCUS Program database including at a minimum:
    a. The number of prescribers enrolled in the FOCUS Program and completed Prescriber Knowledge Assessments
    b. The number of patients enrolled in the FOCUS Program and completed counseling call events
    c. ONSOLIS Month-to-Date Sales (Distribution) Report
    d. Dispensing activity which provides shipment confirmation and authorization to dispense data from enrolled FOCUS pharmacies

2. Results of any prescriber, pharmacy, wholesaler, and vendor audits conducted and corrective actions taken during the reporting period.

3. Results of any surveys conducted of prescribers understanding and knowledge of the critical elements of the prescriber education for the FOCUS Program.

4. Results of any surveys conducted of patients understanding and knowledge of the serious risks of Onsolis.

5. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

6. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

7. Results of surveillance and monitoring activities for abuse, misuse, and overdose including:
    a. Signals that indicate misuse, abuse, overdose, addiction, or diversion
    b. Signals that indicate serious adverse events or deaths related to inappropriate prescribing or other prescriber misuse of Onsolis

8. Drug Utilization Data including the following information:
    a. Data from flagged prescriptions from more than 2 prescribers to the same patient
    b. Any cases of prescribing and dispensing to non-opioid tolerant patients
    c. Extent of shipment delays where the patient received drug >5 business days after the original prescription was received by the pharmacy

The components of the REMS Assessment Plan has been included in the draft approval letter for Onsolis.

4. DISCUSSION

The REMS proposal calls for dispensing of Onsolis through a program that involves specialty pharmacies. The specialty pharmacies will ship Onsolis via traceable courier to enrolled patients only after all criteria are met:

1) prescription is written by enrolled prescribers for an enrolled patient,

2) the prescriber faxes the prescription to a central pharmacy,

3) FOCUS pharmacy verifies that the prescriber and patient are enrolled, that the patient has received a FOCUS program counseling call (for the initial prescription) to review the safe use condition and to ensure that their prescriber has counseled the patient, and

4) that the original, hardcopy prescription for Onsolis has been received.

Additional components includes a plan to re-counsel and re-enroll prescribers, patients, and pharmacies when there are substantial changes to the FOCUS program or at an interval of at least every two years. If an enrolled patient transfers to another prescriber, the patient and new prescriber will complete a new FOCUS program patient enrollment form.

The FOCUS program includes a plan to monitor 1) a database of enrolled entities, 2) the distribution of Onsolis to make sure it is only shipped to active pharmacies, 3) dispensing by pharmacies to ensure only active patients receive Onsolis and active prescribers are prescribing Onsolis, and 4) a detailed plan for auditing to make sure the program is implemented as directed. The plan will require FOCUS pharmacies to keep records of delays where the patient received drug more than 5 business days after the prescription was received by the pharmacy. The reasons for the delay will be investigated and reviewed monthly.

5. CONCLUSION

The REMS proposal dated May 22, 2009 contains the agreed REMS components including a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments. The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals.

We believe that a REMS comprised of these components will appropriately mitigate the risks of Onsolis including the risk of overdose, abuse, addiction and serious complications due to medication errors.

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/s/

Mary Dempsey
6/24/2009 07:44:40 AM
DRUG SAFETY OFFICE REVIEWER
Onsolis REMS review checked inot DFS 6-22-09 this is to link to AZ Dec 12, 2008