CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-266

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-266

COMPLETE RESPONSE

BioDelivery Sciences International, Inc.
801 Corporate Center Drive
Suite 210
Raleigh, NC 27607

Attention: David T. Wright, PhD, RAC
Director, Regulatory Affairs

Dear Dr. Wright:

Please refer to your New Drug Application (NDA) dated October 31, 2007, received October 31, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Onsolis (fentanyl buccal soluble film) 200, 400, 600, 800, and 1200 mcg for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for the underlying persistent cancer pain.

We acknowledge receipt of your amendments dated November 19, and 21, 2007, January 24, February 22, and 28, March 11, and 25, April 1, 3 (2), 16, and 21, May 7, and 9, June 9, 12, 25, and 26, July 8, and August 5 (2), 2008.

We also acknowledge receipt of your amendments dated August 19, and 22, 2008, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

You submitted a proposed Onsolis Risk Minimization Action Plan (RiskMAP) on October 31, 2007, and subsequent amendments to the RiskMAP on March 20, April 11, and May 7, 2008. Before this NDA may be approved, you must submit a proposed Risk Evaluation and Mitigation Strategy (REMS), described below, in place of the RiskMAP.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require submission of a Risk Evaluation and Mitigation Strategies (REMS) if FDA has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Onsolis (fentanyl buccal soluble film) to ensure that the benefits of the drug outweigh the risks of overdose, abuse, addiction, and serious complications due to medication errors. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Onsolis poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Onsolis. FDA has determined that Onsolis is a product that has serious risks (relative to benefits) of which patients should be made aware as information concerning the risks could affect patients' decisions to use, or continue to use Onsolis. FDA has also determined that Onsolis is a product for which a Medication Guide could help prevent serious adverse events. Under 21 CFR Part 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Onsolis.

Communication Plan: We have determined that a communication plan targeted at healthcare providers who are likely to prescribe Onsolis and pharmacists who are likely to dispense Onsolis will support implementation of the elements of your REMS. The communication plan must include the dissemination of information about labeling, including the Medication Guide, and the elements of the REMS, to encourage implementation by health care providers of relevant portions of the REMS, and to explain certain safety protocols.

The communication plan must include at a minimum the following:

Dear Healthcare Provider/Pharmacist Letters to be distributed at product launch. Your communication plan should state specifically the types and specialties of healthcare providers and pharmacists to which the letters will be directed. Append the draft letters and other communication materials to the proposed REMS.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks that will be listed in the labeling of the drug. In addition, we have determined that the Medication Guide and the Communication Plan discussed above are not sufficient to mitigate the serious risks. Your proposed REMS must include tools to manage these risks, including, at a minimum, the following:

1. A plan to ensure that Onsolis will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A) through the certification process described below. At a minimum, the plan shall require that:

   a. Prescribers are trained about:

      (1) proper patient selection

(2) appropriate product dosing and administration

(3) general opioid use including information about opioid abuse and how to identify patients who are at risk for addiction

(4) the risks of Onsolis including:

(a) the risk of overdose caused by giving Onsolis to someone for whom it has not been prescribed

(b) the risk of overdose due to prescribing Onsolis to opioid non-tolerant patients

(c) the risk of addiction from exposure to Onsolis

(5) how to enroll patients into the REMS program

b. Prescribers have obtained certification by attesting to the following:

(1) I have been trained and understand the risks and benefits of chronic opioid therapy.

(2) I understand Onsolis can be abused and this should be considered when prescribing or dispensing Onsolis in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

(3) I understand that Onsolis is indicated only for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for the underlying persistent cancer pain.

(4) I understand that Onsolis is not bioequivalent with any other oral transmucosal fentanyl citrate products and therefore should not be converted from other oral transmucosal fentanyl citrate products on a microgram per microgram basis.

(5) I will prescribe Onsolis after ensuring documentation of safe use conditions described below.

(6) I will enroll patients into the REMS program.

c. The sponsor will maintain a list of the prescribers who have obtained the certification, and provide the list to those needing to verify that a prescriber has obtained the required certification.

d. Prescribers will be retrained and recertified periodically, at a specified interval.

2. A plan to ensure that Onsolis is only dispensed by pharmacies, practitioners, or healthcare settings (e.g., hospitals) who are specially certified under 505-1(f)(3)(B) by requiring that:

   a. Onsolis is dispensed through certified pharmacies, practitioners, or healthcare settings. To obtain certification, a pharmacy, practitioner, or healthcare setting must agree to:

      (1) train their staff about the REMS procedures and education materials

      (2) dispense Onsolis after ensuring documentation of safe use conditions described below

      (3) not substitute Onsolis for other oral transmucosal fentanyl citrate products

   b. The sponsor will maintain a list of the pharmacies, practitioners, or healthcare settings who have obtained the certification, and provide the list to those needing to verify that the required certification has been obtained.

   c. Pharmacies, practitioners, or healthcare settings will be retrained and recertified periodically, at a specified interval.

3. A plan to ensure that the drug is dispensed to patients with documentation of the following safe use conditions under 505-1(f)(3)(D):

   a. A prescriber must document that he or she:

      (1) has enrolled each patient in a program by obtaining at the time of first prescribing and on a specific periodic frequency thereafter a signed physician-patient agreement form that documents safe use conditions, i.e., patients being prescribed Onsolis are opioid tolerant; patients require chronic opioid around-the-clock analgesia for moderate to severe pain; patients have been counseled about the risks and benefits and appropriate use of Onsolis, and about the risk of overdose due to giving Onsolis to someone for whom it has not been prescribed; and patients have been provided and reviewed the Medication Guide

      (2) will provide a copy of the enrollment form to the sponsor

   b. The sponsor will maintain a list of the patients who have been enrolled and verify patient enrollment to those needing to verify that a patient has been or has not yet been enrolled. The sponsor will provide a unique patient identifier when each patient is enrolled. Patients will always be tracked using this unique identifier so that the sponsor can monitor Onsolis prescribing for each patient.

c. Pharmacies, practitioners, or healthcare settings that dispense Onsolis must document that the drug has been dispensed under the following safe use conditions:

(1) The pharmacy, practitioner or healthcare setting has dispensed Onsolis only to enrolled patients, based on a valid prescription from a certified prescriber (enrolled patients and certified prescribers to be determined from a list maintained by the sponsor).

(2) The pharmacy, practitioner or healthcare setting has ensured that patients have been on an appropriate dose of opioid medication on an around-the-clock regimen for an adequate amount of time to assure that they are opioid-tolerant.

(3) The pharmacy, practitioner or healthcare setting has counseled patients on appropriate product use.

(4) The pharmacy, practitioner or healthcare setting has provided each patient a Medication Guide with each prescription and instructed the patient to read it.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require that the drug be dispensed to patients with documentation of safe-use conditions. Include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include:

1. A database of all enrolled entities including prescribers, pharmacies, practitioners, healthcare settings, and patients.

2. A plan to monitor distribution data and prescription data to ensure that only certified pharmacies, practitioners, and healthcare settings are distributing, and dispensing Onsolis and that only certified prescribers are prescribing Onsolis.

3. A plan to monitor and conduct audits of certified pharmacies, practitioners, and healthcare settings to ensure these entities are only dispensing Onsolis after documenting safe use conditions.

Timetable for Assessment: The REMS must include a timetable for assessment of the REMS that shall be no less frequent than every six months for the first 2 years and annually thereafter after the REMS is approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval. The REMS, once approved, will create enforceable obligations.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (See Appendix A). Include information in the template that is specific to your proposed REMS for Onsolis. Additionally, all relevant REMS materials including enrollment forms, baseline data collection forms, and any educational materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS and should include the following sections as well as a table of contents:

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
    a. Medication Guide and/or Package Insert
    b. Communication Plan
    c. Elements to Assure Safe Use
    d. Implementation System
    e. Timetable for Assessment of the REMS
    f. Information Needed for Assessments
4. Other Relevant Information

Information needed for the assessment must include but may not be limited to, the following:

1. a survey of patients' or healthcare providers' understanding of the serious risks of Onsolis
2. a report on the status of the training and certification program for healthcare professionals
3. an evaluation of the effectiveness of the REMS program through:
    a. a claims study to evaluate Onsolis utilization patterns including opioid-tolerant utilization patterns before and after implementation of your REMS

b. an analysis and summary of surveillance and monitoring activities for abuse, misuse, and overdose and any intervention taken resulting from signals of abuse, misuse, and overdose

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

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

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

NEW PROPOSED REMS FOR NDA 22-266

On the first page of subsequent submissions related to an already-submitted proposed REMS, prominently identify the submission by including this wording in bold, capital letters at the top of the letter:

PROPOSED REMS-AMENDMENT

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   b. Present tabulations of the new safety data combined with the original NDA data.

   c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Kimberly Compton, R.Ph., Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sharon H. Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research

Enclosures-

Appendix A-REMS Template
Package Insert and Medication Guide

16 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)