CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-266

OTHER 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 23, 2008
To:	Bob A. Rappaport, M.D., Director **Division of Anesthesia, Analgesia and Rheumatology Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (PPI, MG, or PIFU)
Drug Name(s):	Onsolis (fentanyl buccal soluble film)
Application Type/Number:	NDA 22-266
Applicant/sponsor:	BioDelivery Sciences International
OSE RCM #:	2007-2577

1 INTRODUCTION

BioDelivery Sciences International submitted an Original New Drug Application, NDA 22-266 for ONSOLIS (fentanyl buccal soluble film). ONSOLIS is a potent opioid analgesic (schedule II) 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.

OSE has deferred review and comment on a proposed RiskMAP until the sponsor submits a Risk Evaluation and Mitigation Strategy (REMS) comparable to what is being requested for the marketed oral transmucosal fentanyl products. Refer to the OSE deferral memo dated July 17, 2008. However, the review division requested that the Patient Labeling and Education team proceed with review of the Medication Guide at this time. This review is written in response to that request.

2 MATERIAL REVIEWED

- Draft Professional Information (PI) submitted on June 20, 2008 and further revised by the review division and provided to DRISK on July 2, 2008.
- Draft Medication Guide (MG) submitted on June 20, 2008 and further revised by the review division and provided to DRISK on July 2, 2008.
- Fentora MG approved on February 7, 2008.
- Actiq MG approved on February 7, 2007
- OSE Deferral for Proposed RiskMAP dated Juy 17, 2008

3 DISCUSSION

The purpose of Medication Guides is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 7.9, and a Flesch Reading Ease score of 59.3. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- made the MG consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).
- Compared the proposed MG primarily to the approved MG for Fentora and also to the approved MG for Actiq.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts

such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. Each ONSOLIS film is individually wrapped in a child-resistant, protective foil package. These foil packages are packed 30 per carton. The sponsor should clarify how they intend to insure distribution of the MG to patients with each prescription. Unless all ONSOLIS is packaged in unit-of-use packaging with the MG enclosed, it is highly unlikely that patients will receive the MG.
2. We have strengthened language in the MG to be consistent with the language in the ONSOLIS PI and the Fentora MG regarding the definition of opioid tolerant as "regularly using other opioid pain medicines around-the-clock for constant cancer pain and you body is used to these medicines." The sponsor's proposed language implies that patients have to be taking opioids every day and that it does not have to be constant pain.
3. In the section "What is ONSOLIS?" we have added a bullet at the end of the section stating "It is not known if ONSOLIS is safe and effective in children under the age of 18" to be consistent with PI section 8.4.
4. In the section "Who should not use ONSOLIS?" we deleted the word [redacted] from the original 4th bullet [redacted] b(4)
5. In the section "How should I use ONSOLIS?":
   - We have further clarified the 3rd sub-bullet instructing patients to use ONSOLIS only one time for each episode of breakthrough cancer pain and to separate each dose by 2 hours.
   - We have clarified the 4th sub-bullet to instruct patients not to use the product for more than 4 episodes of breakthrough cancer pain in one day.
   - We added a bullet instructing patients how to correctly use more than one ONSOLIS film at one time if directed to do so by their doctor.
6. Label the figures and reference them in the MG text.
7. The sponsor should clarify the percentage cutoff used in listing side effects in the MG and update the list as appropriated for consistency with section 6.1 of the PI.
8. We have added the following statement to the end of the section, "General Information about TRADENAME":

   Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

   This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008).

9. We have added two bullets at the end of the section "How should I store ONSOLIS?" to instruct patients not to freeze ONSOLIS and to protect if from moisture.
10. We have added language to the last bullet regarding help with disposal of ONSOLIS to make it consistent with the language in the PI, instructing patients to call their local Drug Enforcement Agency (DEA) if needed.
11. We have revised the first sentence of the section "General information about ONSOLIS" to reflect required verbatim language for MGs according to 21 CFR 208.20 (b) (8) (1).

Please let us know if you have any questions.

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

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7/23/2008 05:05:25 PM
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DRUG SAFETY OFFICE REVIEWER

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:	January 10, 2008
To:	Bob Rappaport, MD, Director Division of Analgesics, Anesthetics, and Rheumatology Products
Thru:	Linda Kim-Jung, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Kristina C. Arnwine, PharmD, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	DMETS Label and Labeling Review
Drug Name(s):	BEMA (Fentanyl Bio-erodible Mucoadhesive——— b(4)
Application Type/Number:	IND#: 62,864, NDA# 22-266
Submission Number:	N/A
Applicant/sponsor:	BioDelivery Sciences International
OSE RCM #:	2007-1819 and 2007-2021

EXECUTIVE SUMMARY

BEMA Fentanyl is similar in design to other oral transmucosal fentanyl products (i.e. Fentora and Actiq). Thus, DMETS anticipates the risks associated with BEMA Fentanyl will be similar to the risks and medication errors seen with Fentora and Actiq. Our analysis of the labels and labeling for BEMA Fentanyl indicate that revisions are necessary to help ensure safe use of this product and to ensure that all oral transmucosal fentanyl products have consistent warnings regarding all associated risks.

1 BACKGROUND

1.1 INTRODUCTION

This memorandum is in response to an August 20, 2007 request from your Division for a review of the container label and carton labeling for BEMA Fentanyl patches. The proposed proprietary tradename, Onsolis, will be reviewed under separate cover (OSE Review #1849).

1.2 PRODUCT LABELING

BEMA Fentanyl is indicated for the management of breakthrough pain in cancer patients 18 years and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The usual dose of BEMA Fentanyl is titrated to a dose that provides adequate analgesia without undue side effects. BEMA Fentanyl should be limited to treating four or fewer pain episodes per day. BEMA Fentanyl is supplied in 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg units.

2 METHODS AND MATERIALS

Container labels and carton labeling submitted on August 7, 2007 [redacted] b(4)

3 RESULTS

3.1 Container Label

3.1.1 The proposed container label does not include a warning statement regarding the use of BEMA Fentanyl only in patients that are tolerant to around-the-clock opioid therapy.

3.1.2 The color schemes used for the 600 mcg and 800 mcg product strengths are similar.

3.1.3 The container label does not include dosing instructions highlighting a maximum dose for a single breakthrough pain episode or the time needed between dosing for another breakthrough pain episode.

3.1.4 There is no net quantity statement on the container label.

3.2 Carton Labeling

3.2.1 See comments 3.1.1. and 3.1.2.

3.2.2 The pharmacist checklist is not prominent enough to draw attention to the important information contained therein.

3.2.3 As currently presented, the information in the pharmacist checklist, and the manner in which the information is presented, are not consistent with the information contained in the pharmacist checklist for other oral transmucosal fentanyl citrate products.

3.2.4 The net quantity is not presented in a conventional format.

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4 DISCUSSION

In the review of the container labels and carton labeling of BEMA Fentanyl, DMETS has identified areas where improvements can be made in the interest of minimizing user error and maximizing patient safety. We are most concerned with the potential for use in non-opioid tolerant patients for on and off label indications (e.g. migraines), improper dosing, and improper product substitution between the oral transmucosal fentanyl products currently marketed. These concerns are based on the recent events involving serious adverse events and death associated with the use of Fentora (Fentanyl Buccal Tablet), another fentanyl citrate oral transmucosal drug product similar to this proposed drug. The adverse events and deaths associated with the use of Fentora were a result of improper selection of patients, improper dosing, and improper product substitution. Because BEMA Fentanyl is similar in design we anticipate the same types of problems occurring with this product as well.

What is more concerning with the BEMA product as compared to the other oral transmucosal products is that BEMA Fentanyl is considerably more potent despite having identical product strengths. We are concerned that healthcare practitioners and patients will not understand these differences and think these products are bioequivalent. This could lead to improper product substitution or improper dosing leading to serious outcomes including death. The bioavailability of BEMA Fentanyl when compared to Actiq, resulted in 40% greater exposure at identical doses. When comparing Fentora to Actiq, Fentora resulted in 30% greater exposure at identical doses[1]. Therefore, it is a reasonable assumption that the maximal plasma concentrations of BEMA Fentanyl and Fentora differ at identical doses as well. This assumption is based on the lessons learned with dosing conversions between Fentora and Actiq. Additionally, because of the reported incidences of oral ulceration associated with Fentora, DMETS anticipates the possibility of patients requesting to be converted from Fentora to BEMA Fentanyl in an attempt to avoid oral ulceration. Thus, educating prescribers, pharmacists, and patients regarding the comparative bioavailabilities of BEMA Fentanyl, Fentora, and Actiq is absolutely imperative. Otherwise we may have an increased number of adverse drug reactions and deaths as a result of this continued misconception of product substitutions and conversions we have encountered with Fentora.

The potential for overdose if prescribers and/or patients do not understand how to appropriately re-dose during a single breakthrough pain episode is also a major concern based on the postmarketing overdoses seen with Fentora. Similar to Fentora, if the initial dose of BEMA

[1] Fentora Package Insert, approved April 2007

Fentanyl is not successful in treating the breakthrough pain episode, a patient may administer a second dose of BEMA Fentanyl 30 minutes after the first dose. The current labels do not include a warning about maximum dosing during a single episode. This needs to be highlighted on the container and insert labeling. This information should be part of the education as well.

In addition to lacking the warning regarding the maximum dose for a single breakthrough pain episode, the current labels do not adequately address inappropriate substitution with other oral transmucosal fentanyl citrate products (i.e. Fentora, Actiq), use in inappropriate patients and inappropriate dosing which can all lead to serious adverse events and death. Thus, the same revisions, warnings, and key safety messages incorporated into the Fentora labeling should be applied to BEMA Fentanyl labeling as well.

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5 CONCLUSIONS AND RECOMMENDATIONS

The current labels of BEMA Fentanyl inadequately address the safety issues with respect to use in appropriate patients, inappropriate substitution with other oral transmucosal fentanyl citrate products, and inappropriate dosing. Labels and labeling for BEMA Fentanyl must be revised to include appropriate warning and instructions to educate everyone involved in the medication use process, including prescribers, pharmacists, and patients/caregivers, regarding the risks associated with the use of BEMA Fentanyl.

b(4)

With regard to the established name, DMETS recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (the project manager assigned to the LNC) and the assigned ONDQA Chemist for further guidance.

In order to decrease the potential for user error that we have seen with Fentora, we recommend the following revisions be implemented.

5.1 CONTAINER LABEL

5.1.1 Include the statements

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and "

in red font inside the boxed warning.

5.1.2 Revise the color scheme(s) used for the 600 mcg and/or 800 mcg so that the colors are more distinct from one another.

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BEMA Fentanyl 600 mcg Carton BEMA Fentanyl 800 mcg Carton

5.1.3 Include explicit dosing instructions on the container label specifically highlighting a maximum dose for a single breakthrough pain episode and the time needed between dosing for another breakthrough pain episode.

5.1.4 Include the net quantity (i.e. 1 system) on the container label.

5.2 CARTON LABELING (28 UNITS AND 112 UNITS)

5.2.1 See comments 4.1.1 and 4.1.2.

5.2.2 Box the pharmacist checklist and relocate it to the principal display panel in order to increase its prominence.

5.2.3 Revise the first item in the pharmacist checklist to read "[redacted]" b(4)

5.2.4 Revise the second item in the pharmacist checklist to read "[redacted]" b(4)

5.2.5 Revise the font color of the first two items in the pharmacist checklist in order to increase their prominence (e.g. red font).

5.2.6 Per CFR 21 208.24(d), revise the fourth item in the pharmacist checklist to read "[redacted]" b(4)

5.2.7 Revise the net quantity to read "[redacted]". b(4)

[redacted] b(4)

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, project manager, at 301-796-0723.

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/s/

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