

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-266

SUMMARY REVIEW



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY
PRODUCTS**

Summary Review for Regulatory Action

Date	June 16, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA#	22-266
Applicant Name	BioDelivery Sciences, International
Date of Submission	December 9, 2008
PDUFA Goal Date	June 12, 2008
Proprietary Name / Established (USAN) Name	Onsolis Fentanyl buccal soluble film
Dosage Forms / Strength	Oral transmucosal film; 200 mg, 400 mg, 600 mg, 800 mg and 1200 mg
Proposed Indication	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
Action:	Approval

N 22-266

1

Onsolis

Division Director Review and Summary Basis for Approval Action

June 16, 2009

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Ellen Fields, M.D. M.P.H.; Elizabeth Kilgore, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Gary Bond, Ph.D.; Adam Wasserman, Ph.D.
CMC Review	Xavier Ysern, Ph.D.; Ali Al-Hakim, Ph.D.;
Microbiology Review	N/A
Clinical Pharmacology Review	David Lee, Ph.D.; Suresh Doddapaneni, Ph.D.
CSS	Lori Love, M.D., Ph.D.; Silvia Calderon, Ph.D., Mike Klein, Ph.D.
DDMAC	Michelle Safarik, PA-C; Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D.
DSI	Sherbet Samuels, R.N., M.P.H.; Constance Lewin, M.D., M.P.H.
CDTL Review	Sharon Hertz, M.D.
OSE/DMEPA	Kristina Arnwine, Pharm.D.
OSE/DPII	Afrouz Nayernama, Pharm.D.
OSE/DRISK	Jeanne Perla, Ph.D.; Jeanine Best, M.S.N., R.N., P.N.P.; Mary Dempsey; Marcia Britt, Ph.D.; Jodi Duckhorn, M.A.; Brian Gordon, M.A.; Sharon Mills, B.S.N., R.N., C.C.R.P.; Mary Willy, Ph.D.; Claudia Karwoski, Pharm.D.
Office of Compliance/DRMS	Agnes Plante, B.S.N., R.N.; Suzanne Barone, Ph.D.

OND=Office of New Drugs
 CSS=Controlled Substances Staff
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DRISK= Division of Risk Management
 DPII=Division of Pharmacovigilance II
 CDTL=Cross-Discipline Team Leader
 DRMS=Division of Risk Management and Surveillance

N 22-266

2

Onsolis

Division Director Review and Summary Basis for Approval Action

June 16, 2009

BioDelivery Sciences, International submitted their original NDA for Onsolis on October 31, 2007. On August 25, 2008, a Complete Response letter was issued to the sponsor and a **thorough Division Director's Review and Summary Basis for Action** was filed by Dr. Sharon Hertz (Dr. Hertz's review is attached to this review and denoted Appendix 1). The letter and Dr. Hertz's review summarized the approvability of this product based on an adequate demonstration of efficacy, safety and product quality. The only outstanding deficiency in the application was noted to be the finalization of an acceptable Risk Evaluation and Mitigation Strategy (REMS) to address the risks of misuse, abuse and overdose associated with this potent fentanyl transmucosal drug product. The basis for establishing a REMS for this and similar products, and the components that would be necessary to provide an adequate REMS **are explicated both in Dr. Hertz's review and in the REMS memo** for this application (attached to this review and denoted Appendix 2). This review will focus solely on the adequacy of the sponsor's REMS submission in fulfilling the requirements listed in the above noted documents.

As discussed in Dr. Hertz's REMS memo of August 4, 2008, the approval of Onsolis could result in the use of this product by up to _____, if limited to cancer patients already on around-the-clock therapy with a potent opioid for their cancer-related pain requiring additional opioid treatment for episodes of breakthrough pain. While there are two previously approved oral transmucosal fentanyl products with the same indication, Actiq and Fentora, Onsolis would provide a new drug delivery system that would potentially result in an improved safety profile for this class of products. Onsolis is not likely to cause the dental caries seen in some patients treated with Actiq; nor is it likely to cause the elevations in glucose levels in some diabetic patients treated with Actiq. Also, based on the clinical study experience, Onsolis is unlikely to cause the mucosal ulcerations seen in some patients using Fentora. The duration of treatment will vary from days in pre-terminal patients to months in patients with longer survival prognoses. There are serious and life threatening adverse events associated with the use of any of these extremely potent oral transmucosal fentanyl products including respiratory failure and CNS depression which occur primarily when the products are not used properly. In addition, Dr. Hertz notes that Onsolis poses a serious and significant **public health concern due to fentanyl's high propensity to be sought out by abusers**, with resultant diversion, addiction, overdose and death.

b(4)

Actiq was approved in 1998 under Subpart H of the Food, Drug and Cosmetic Act which allowed the Agency to incorporate an extensive Risk Management Plan (RMP) into the **product labeling**. However, both Actiq's RMP and the original Risk Minimization Action Plan (RiskMAP) implemented for Fentora failed to meet their stated objectives. In particular, **Fentora's RiskMAP failed to ensure proper patient selection for cancer patients or patients that were opioid-tolerant, and failed to provide adequate education of prescribers and dispensers**. These failures were demonstrated by reports of deaths of patients being treated for migraine headache and chronic low back pain, increasing numbers of opioid non-tolerant patients being prescribed Fentora and by medication errors with improper dose titration and dosing regimen, improper conversion from doses of Actiq, and improper substitution for Actiq. As such, the

Agency has determined that a REMS is necessary to assure the safe use of oral transmucosal fentanyl products.

As outlined in the CR letter, the Onsolis REMS would have to include:

- 1) Medication Guide,
- 2) Communication Plan,
- 2) Elements to Assure Safe Use (ETASU),
- 3) Implementation System,
- 4) Timetable for Submission of Assessments and Information Needed for Assessments.

The sponsor submitted a proposed REMS and a REMS Supporting Document on December 9, 2008. After multiple discussions with the Agency and after the development of multiple iterations of their original REMS proposal, agreement was reached on the adequacy of a final **REMS. The sponsor's REMS program is entitled Full Ongoing Commitment to User Safety, or FOCUS.** The components of the FOCUS program have been summarized on pages 3 through 5 of Dr. Perla's review and are reproduced below along with her discussion of the plan:

Proposed REMS

Goals

The FOCUS Program has the following goals:

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. Informing prescribers, pharmacists, and patients about proper dosing and administration.

3.2. REMS ELEMENTS

- A. *A MEDICATION GUIDE THAT WILL BE DISPENSED WITH EACH Onsolis PRESCRIPTION AND BY THE HEALTHCARE PRESCRIBER*
- B. A Communication Plan that includes the following materials
 1. For Prescribers: Dear Prescriber Letter (provided at product launch); Prescriber Program Overview; prescribing information (PI) and medication guide (MG); Risk Evaluation and Mitigation Strategy (REMS document); Prescriber Enrollment Form (including Prescriber Knowledge Assessment); and Patient Enrollment Form [including Health Insurance Portability and Accountability Act (HIPAA) authorization]
 2. For Pharmacists: Dear **Pharmacist Letter** (provided at product launch); PI and MG; Risk Evaluation and Mitigation Strategy (REMS: this document) b(4)
- C. Elements to Assure Safe Use

N 22-266

4

Onsolis

Division Director Review and Summary Basis for Approval Action

June 16, 2009

1. Education and enrollment of the healthcare providers.
2. Counseling and enrollment of the patient
3. _____ b(4)
4. Education and enrollment of pharmacies that dispense Onsolis

D. Implementation plan

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.

E. TIMETABLE FOR ASSESSMENT

The FOCUS Program is assessed every 6 months for the _____ 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 assessment plan will be placed in the Approval Letter b(4)

a. Assessment Plan

The REMS assessment plan should include but is not limited to 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.

N 22-266
Onsolis

Division Director Review and Summary Basis for Approval Action
June 16, 2009

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.
 - 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

b(4)

DISCUSSION

The Sponsor describes a plan to 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.

b(4)

The plan 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 or regional pharmacy,
- 3) FOCUS pharmacy verifies that the patient and patient are enrolled, that patient has received a FOCUS program counseling call to review the safe use condition and to ensure that their prescriber has counseled the patient,
- 4) that all of the above conditions are met, ONSOLIS is dispensed .

The dispensing FOCUS pharmacy will be required to validate that the prescriber and patient are enrolled and active in the FOCUS program database

Additional components include 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 plan includes a distribution and prescription and data monitoring plan. The plan will have each FOCUS pharmacy will keep a record of delays where the patient received drug more than 72 hours after the prescription was received by the

N 22-266
Onsolis

6

Division Director Review and Summary Basis for Approval Action
June 16, 2009

pharmacy. The reasons for the delay will be investigated and reviewed monthly. The Sponsor plans to compare dispensing records each month compared to FOCUS program records of enrolled prescribers and patients, and patient counseling calls that were performed.

The OSE review team has concluded that the FOCUS program REMS will appropriately mitigate the risks of Onsolis. The DAARP review team agrees that the final FOCUS program REMS is acceptable.

Decision/Action/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment

The sponsor provided adequate evidence to support the efficacy, safety and quality of their product in their initial application. The only outstanding deficiency at that time was the inclusion of an adequate REMS to assure the safe use of this highly potent oral transmucosal fentanyl product. After numerous interactions with the Agency, the sponsor has provided an acceptable REMS in their proposed FOCUS program.

While the ETASU in the FOCUS program provide a significant level of restriction to the prescribing and dispensing of Onsolis, I am in full agreement with the sponsor and the FDA review team that these **restrictions are essential to the product's safe use**. Fentanyl is an extremely potent opioid that can result in overdose and death in even small quantities when used by opioid non-tolerant patients, or even when misused by opioid-tolerant patients. The Onsolis formulation of fentanyl is not equally bioavailable to the previously approved and currently marketed products, Actiq and Fentora, allowing for dosing and substitution errors and there have been reports of inappropriate substitutions of one of these products for the other that have resulted in serious morbidity. Evidence exists from long-term surveillance of these previously approved oral transmucosal fentanyl products that they are misprescribed and even at times prescribed to opioid non-tolerant patients. In addition All of these events have occurred in the setting of extensive risk management programs. However, these RMPs did not have requirements for restricted prescribing and dispensing based on adequate patient, prescriber and dispenser training and certification. In addition, fentanyl is one of the most highly sought after opioids by abusers. Taken together, these concerns will require that the sponsor be able to assure that Onsolis is properly prescribed and dispensed, and that patients, prescribers and dispensers are adequately trained in the proper use of the product.

The use of a limited number of specialty pharmacies and the incorporation of patient, prescriber and dispenser registries are particularly important ETASU for Onsolis. These features will allow assurance that all parties have been adequately educated, and that only

N 22-266

Onsolis

Division Director Review and Summary Basis for Approval Action

June 16, 2009

those prescribers, dispensers and patients with adequate training will be able to prescribe, dispense and obtain product. Ongoing reassessment of the adequacy of training and of the proper implementation of the FOCUS program will help to assure that laxity in these parameters does not occur over time and that any signals of increasing misuse or abuse of the product will be noted in a timely manner. An additional feature that is particularly important is that each dispensing pharmacy will be using scripted educational programs for patients. This is far superior to the educational input that would be likely to occur at a busy community pharmacy.

It is also important, however, to assure that patients who do require this medication continue to have timely access to it. In some ways, the FOCUS program may actually improve patient access. For instance, under the FOCUS program the product will be shipped by courier directly from the specialty pharmacy to the **patient's home**. **As many cancer patients are** debilitated and unable to travel even short distances, or live long distances from pharmacies that stock this type of potent opioid, this will provide a considerable advantage. While there are potentially short delays built into the delivery system, these delays are also likely to occur when obtaining drug at community pharmacies; and as long as there is proper planning on the part of prescribers and patients or their caregivers, I do not see this as a major impediment to reasonable access.

- **Recommendation for Postmarketing Risk Management Activities**

No additional Post-marketing risk management activities are necessary at this time. As periodic assessments or intermittent signals of misuse, abuse and/or overdose of Onsolis become available, the Agency will carefully review the data and consider the need for additional risk management elements.

- **Recommendation for other Postmarketing Study Commitments**

No post-marketing study commitments are required for this application other than the pediatric program which will be deferred until a reasonable safety profile has been established in adults in the postmarketing period.