8. Advisory Committee Meeting

No advisory committee meeting was held for this application.

9. Pediatrics

A Written Request was issued on June 28, 2007. The results of pediatric studies were not submitted, and for the purposes of this application, pediatric studies may be deferred.

10. Other Relevant Regulatory Issues

Ms. Sherbet Samuels provided the consultation from the Division of Scientific Investigations. Two study sites with a large number of enrolled subjects were inspected. No significant regulatory violations were found.

A consultative review was performed by Dr. Lori Love of the Controlled Substances Staff. In the summary of the abuse, misuse and diversion data, it was noted that there were a number of cases where the study drug was not returned including five cases following a patient's death, (these deaths were not caused by the study drug, see Dr. Field's review), three cases of study discontinuation due to adverse events, two cases of study withdrawal due to noncompliance, three cases of consent withdrawn and one case of a subject lost to follow up. One case of misuse by the daughter of a patient was reported, without apparent adverse outcome.

The recommendations from this review are:

- Fentanyl from Onsolis is rapidly absorbed, and highly bioavailable by the transmucosal route. Consequently, the potential risks associated with this new formulation are expected to be as high as or greater than those posed by other marketed transmucosal fentanyl products (e.g., Actiq).
- Because the risks are serious and potentially life threatening, a REMS has been recommended to assure that the benefits of Onsolis outweigh potential risks.

11. Labeling

Ms. Michelle Safarik performed a review of the product labeling, medication guide, carton and container labeling for the Division of Drug Marketing and Communication. She had no comments for the carton and container labeling. Ms. Safarik provided a number of comments for the package insert and medication guide that have been conveyed to the applicant and incorporated into the labeling.

Dr. Kristina Arnwine performed the proprietary name risk assessment and has found no objection to the name ONSOLIS.

12. Recommendations/Risk Benefit Assessment

Recommended regulatory action

Complete Response

Risk Benefit Assessment

For the proposed indication, 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, the risk of serious adverse event is outweighed by the benefit as long as the general and particular risks associated with this formulation are appropriately addressed. This will entail the creation and maintenance of a REMS that highlights the differences in pharmacokinetic properties and dosing for BEMA Fentanyl as compared to Actiq and Fentora so that prescribers and patients understand that these are not different names for the same product. The REMS will also need to emphasize the need for proper patient selection, safe use of the product by patients, limiting exposure and risk to household contacts, and protecting the product from misuse and theft. These important points and the elements of the REMS associated with each are detailed below.

Recommendation for Postmarketing Risk Management Activities

A comprehensive REMS is required to avoid the postmarketing problems found following the approval of Fentora. In addition, the labeling and REMS must provide clear warnings about the differences in bioavailability between BEMA Fentanyl and Actiq and Fentora. The REMS is to include the following elements, written in the format to be conveyed to the applicant.

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. 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 FENTORA. Pursuant to 21 CFR Part 208, FDA has determined that FENTORA 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 FENTORA. FDA has determined that FENTORA is a product that has serious risks (relative to benefits) of which patients should be made aware of because information concerning the risks could affect patients' decision to use, or continue to use FENTORA. FDA has also determined that FENTORA is a product for which patient labeling could help prevent serious adverse events. Your approved Medication Guide will now be considered part of the REMS in accordance with 505-1.

Communication Plan: We have determined that a communication plan to healthcare providers who are likely to prescribe FENTORA will support implementation of the elements

of your REMS. At the time of the REMS approval, implement a communication plan to healthcare providers and pharmacies to support implementation of this REMS. Include the following in your communication plan:

- Dear [redacted] Pharmacy Letter b(4)
  - A description of who will be the audience for the communication plan, stating specifically the types and specialties of the healthcare providers to which the communications will be directed.
  - To be distributed on product launch

Elements to Assure Safe Use: As one element of a REMS, FDA may require the development of elements to assure safe use in accordance with 505-1. We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of this drug and your current RiskMAP tools have not effectively mitigated these risks. In addition, we have determined that the Medication Guide and the Communication Plan discussed above are not sufficient to mitigate the serious risks. The elements to assure safe use must include the following:

a. A plan to certify that healthcare providers who prescribe the drug have particular training and knowledge about the risks of FENTORA, the need for proper patient selection, appropriate product dosing and administration, and commit to counseling patients on the risks and benefits of FENTORA.

i. The risks to be elucidated are to include:
   a) the risk of overdose caused by giving FENTORA to someone for whom it has not been prescribed
   b) the risk of overdose due to prescribing FENTORA to opioid-non-tolerant patients
   c) the risk of abuse and addiction from exposure to a Schedule II opioid

ii. The information necessary for safe use is to include:
   a) proper patient selection, including opioid tolerance
   b) appropriate product dosing and administration
   c) that FENTORA is not bioequivalent with any other oral transmucosal fentanyl citrate (OTFC) products and therefore should not be converted from other OTFC products on a mcg per mcg basis
   d) general opioid use including information about opioid abuse, how to identify patients who are at risk for addiction, how to identify patients who are be seeing multiple prescribers for the purpose of obtaining FENTORA for abuse, the use of doctor-patient contracts and random urine drug screening, the history of FENTORA abuse and the targeting of FENTORA for theft by household contacts for the purpose of abuse

iii. Physicians must commit to counseling patients on the risks and benefits of FENTORA and on how to use the product safely. This counseling is to include:
   a) reviewing the Information for Patients section of the package inserts with patients when the prescription is written
   b) strongly advising patients to read the Medication Guide each time a prescription is written for FENTORA

iv. The opportunity to obtain such training or certification as previously described shall be available to any willing provider from a frontier area in a widely available training or certification method (including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider).

b. A plan to ensure and certify that pharmacies and health care settings that dispense FENTORA are specially certified (the opportunity to obtain such certification shall be available to any willing provider from a frontier area); such that they are staffed by individuals knowledgeable about the risks of FENTORA, how to identify drug seeking behavior, and the importance of dispensing a Medication Guide with each FENTORA prescription filled. In addition, before dispensing FENTORA, the pharmacists must ensure that, 1) patients are enrolled in a patient registry; 2) counseled on appropriate product use; 3) a Medication Guide is dispensed and patients are instructed to read it ; and 4) 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 opioid tolerant; 5) there is no therapeutic substitution.

c. A plan to ensure that each patient using the drug will be enrolled in a registry. This patient registry will provide a unique patient identifier.

d. A plan to ensure and document that the drug is dispensed to patients with evidence or other documentation of safe use conditions. This is to include documentation of enrollment in the patient registry.

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 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.

The Implementation System must include:

- A database of all enrolled entities including pharmacies, prescribers, and patients. The database should link adverse events of interest (adverse events associated with use in opioid nontolerant individuals, misuse of FENTORA, and unintended (accidental) exposure to FENTORA).

- A plan to monitor distribution data and prescription data to ensure that only registered entities are distributing, prescribing, and dispensing FENTORA.
- A plan to monitor pharmacies to ensure these entities are only dispensing FENTORA to patients 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 quarterly for 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.

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

- **Surveys of prescribers', pharmacists' and patients' knowledge, attitudes, and behavior** regarding the serious risks and safe use of FENTORA.
- A report on the status of the training and certification program for healthcare professionals.
- An evaluation of the effectiveness of the REMS program, through a claims study to evaluate FENTORA utilization patterns including opioid-tolerant utilization patterns before and after implementation of your REMS.
- An analysis and summary of surveillance and monitoring activities for abuse, misuse, and diversion and any intervention taken resulting from signals of abuse, misuse, and diversion.
- A narrative summary and analysis of adverse events associated with use in opioid nontolerant individuals, misuse of FENTORA, and unintended (accidental) exposure to FENTORA).
- Summary data from your implementation system (distribution data, documentation of safe use conditions) including person years of exposure and number of patients.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

- Recommendation for other Postmarketing Study Commitments

The applicant has received a deferral for pediatric studies pending completion of studies to respond to a Pediatric Written Request. These studies will also fulfill the requirements under PREA.

- Recommended Comments to Applicant

See the REMS comments above.

Appendix 2

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

MEMORANDUM

DATE: August 4, 2008

TO: File, NDA 22-266

From: Sharon Hertz, M.D.
Deputy Divison Director

RE: Risk Evaluation and Mitigation Strategy (REMS) Requirements

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Onsolis outweigh its risks. In reaching this determination we considered the following:

A. The proposed indication could result in use of the product in a population of ——— patients. b(4)
B. The patients for this product are cancer patients with pain that cannot be adequately controlled using around-the-clock oral or transdermal opioids alone. Many of these patients have multiple concurrent complications of their underlying disease and therapy.
C. The expected benefit of the drug to patients is that the delivery system is different than Actiq or Fentora, the first two approved oral transmucosal citrate products. Actiq is formulated as a lozenge on a stick with a high sugar content and has been associated with dental caries and elevations in glucose levels in diabetic patients. Fentora is formulated as a tablet that is placed between the mucosa and gum and has caused local ulcers at the site of administration. Onsolis is formulated as a thin film that adheres to the mucosal surface and has not demonstrated either of the two types of adverse reactions noted with Actiq and Fentora.
D. The expected duration of treatment with the drug will be from days for the sickest patients who are preterminal, to months for patients with less tumor burden and longer prognoses for survival.
E. The most serious of the known adverse events that are related to the use of an oral tranmucosal fentanyl product include death, respiratory depression and CNS depression which occur primarily if the product is not used properly.
F. Onsolis contains the active drug substance fentanyl and is not a new molecular entity.

In addition, based on the clear risk of abuse, overdose and addiction associated with marketed potent opioid analgesics, and pursuant to 21 CFR Part 208, FDA has determined that Onsolis, an opioid analgesic, poses a serious and significant public health concern requiring the distribution of a Medication Guide, the use of a communication plan, and methods to ensure safe use. The Medication Guide, communication plan, and methods to ensure safe use are **necessary for patients' safe and** effective use of Onsolis.

The elements of the REMS will be a Medication Guide, a Communication Plan, methods to ensure safe use, and a timetable for submission of assessments of the REMS.

Sharon Hertz, M.D. (memo must be electronically signed by same signatory authority as letter)
Director, Division of Anesthesia, Analgesia, and Rheumatology Products

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/s/

Bob Rappaport
7/15/2009 09:55:43 PM
MEDICAL OFFICER