CLINICAL REVIEW

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Established Name	Fentanyl buccal soluble film
(Proposed) Trade Name	Onsolis
Therapeutic Class	Opioid analgesic
Applicant	BDSI
Priority Designation	S
Formulation	oral transmucosal
Dosing Regimen	PRN
Indication	Breakthrough cancer pain
Intended Population	Adult cancer patients receiving around the clock opioids with breakthrough pain

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approval action for BEMA Fentanyl for the 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."

Substantial evidence of efficacy was provided by a single adequate and well-controlled efficacy study in cancer patients with breakthrough pain, and supported by supplementary open-label data. Evidence of safety was based on a safety database of approximately 300 cancer patients with breakthrough pain, primarily those enrolled in the an open-label trial, and in addition those who participated in the efficacy trial and a small trial of cancer patients with Grade 1 mucositis.

As a 505(b)(2) application, the above findings also rest in part on the Agency's previous findings of safety and efficacy for Actiq (oral transmucosal fentanyl citrate) which was approved for the same indication in 1998.

There are limitations to the safety data submitted by the Applicant, as follows.

1. Since BEMA fentanyl was being dosed in patients taking around-the-clock opioids for background pain, and the adverse event profile is expected to be similar for all opioids, the determination of causality of adverse events was difficult.

2. The patients enrolled in all trials were extremely ill and were receiving toxic therapies for their underlying conditions. This too made it difficult to assign causality of the adverse events.

3. Because of the cross-over design of the double-blind portion of the efficacy trial, the relationship of the time of the dose of study drug to the time of adverse event was not generally available. Nor was this information available for the open-label phases of the studies.

Despite these limitations, a rigorous review of the safety data did not result in the identification of any unexpected adverse events that could be attributed to the study drug. BEMA Fentanyl appears to be associated with typical opioid-related adverse events, and the vast majority of serious adverse events and deaths were clearly attributable to the patients' underlying disease, treatments, or complications of treatment. A relatively small proportion of patients had application site reactions (oral adverse events) that could be attributed to the use of BEMA Fentanyl.

The major safety concern regarding the use of BEMA Fentanyl is not in relation to its correct use in the intended population. BEMA Fentanyl will be the third oral transmucosal fentanyl product

indicated for the treatment of cancer breakthrough pain, joining Fentora and Actiq. All three products have some of the same dosage unit strengths, yet none are bioequivalent with the others and so are not interchangeable on a microgram by microgram basis. As has become evident with Fentora and Actiq, medication errors with associated adverse events have already occurred. It is extremely important that this risk be mitigated by intense surveillance of the use of BEMA Fentanyl, and the initiation of interventions when necessary.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Applicant submitted a Risk Evaluation and Minimization Strategy (REMS) for BEMA Fentanyl. The REMS includes the following features:

- A program for disseminating important risk and safety information about BEMA Fentanyl to key stakeholders;
- Active and passive surveillance systems to identify, capture, analyze, and report on safety signals associated with intended and unintended use of BEMA Fentanyl; and
- A plan for continually evaluating and reporting on the effectiveness of the RiskMAP and for making appropriate modifications to improve the RiskMAP.

The plan identifies three goals as follows:

1. BEMA Fentanyl should be used only in opioid tolerant patients, and these patients should not experience severe AEs related to its administration;
2. BEMA Fentanyl should not be misused, abused, or diverted; and
3. Accidental ingestion of BEMA Fentanyl should be prevented

The RiskMAP objectives are as follows:

HCPs, patients, and caregivers will be informed about the potential for BEMA Fentanyl diversion and abuse and the importance of safe storage, handling, and use. RiskMAP tools have been designed to effect behavioral changes in these key stakeholders to achieve RiskMAP objectives, as follows:

• HCPs will understand the approved indication of BEMA Fentanyl;

• HCPs will understand the proper population (i.e., opioid tolerant) for use of BEMA Fentanyl;

• HCPs, patients, and caregivers will know the major risks associated with BEMA Fentanyl (i.e., respiratory depression, particularly in opioid non-tolerant individuals, and the risk of death in children who accidentally ingest BEMA Fentanyl)

• HCPs, patients, and caregivers will understand the proper application and dosing of BEMA Fentanyl;

• HCPs, patients and caregivers will know the potential for diversion and abuse; and

• HCPs, patients, and caregivers will understand proper storage, handling, and disposal of BEMA Fentanyl.

The strategies identified in the RiskMAP include:

- Identification of specific key stakeholders (HCPs, patients, and caregivers) to ensure appropriate, tailored risk and safety messages are developed for each specific stakeholder and disseminated at different points along the patient care continuum;

- Development of the educational component, which includes:
  - Design and testing of RiskMAP tools
  - Integration of RiskMAP messages and tools into launch materials to ensure that they will become an integral part of the commercialization process, and
  - Incorporation of redundant educational messages across multiple RiskMAP components to disseminate risk and safety information across all relevant stakeholders and ensure minimization of any gaps in the communication of this information.

- Evaluation of the effectiveness of RiskMAP components and outcomes through feedback mechanisms and monitoring of appropriate databases.

The product labeling will include a MedGuide.

In addition, BEMA Fentanyl will be designated Schedule II under the federal CSA. The product will be subject to strict regulatory controls along its entire distribution pathway to ensure that access to the product is restricted in accordance with regulatory requirements.

An important goal not stated in the REMS as submitted by the Applicant is that BEMA Fentanyl should not be mistaken for the other oral transmucosal fentanyl products. Because of the differences in bioavailability, care must be taken in prescribing these products, and switching between them for the treatment of cancer-related breakthrough pain.

As a consequence of the discussions held at the May 6, 2008 joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee regarding NDA 21-947/s005 (expansion of the indication for Fentora from opioid tolerant cancer patients with BTP to opioid-tolerant non-cancer patients with BTP), the Division is requesting that the Applicant include tools in the REMS that will lessen the likelihood of the prescribing and use of BEMA Fentanyl to the off-label populations. These tools may include both prescriber and patient registries.

The Division of Risk Management (DRISK) in The Office of Safety and Epidemiology (OSE), DDMAC, and DMETS have been consulted to review the Applicant's proposed REMS, and interactions between the Applicant and the Agency are ongoing at this time.

1.2.2 Required Phase 4 Commitments

The Applicant requested a partial waiver for pediatric studies for childrer ___ years old and younger, and a deferral of the Pediatric Assessment required under PREA. The Division will meet with the Pediatric Research Committee (PERC) on July 30, 2008 to review these requests. b(4)

1.2.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

BEMA Fentanyl is a transmucosal formulation of fentanyl developed for the management of breakthrough pain in opioid tolerant cancer patients.

As a reformulation of a well-characterized chemical moiety where there are already two approved products (Actiq® and Fentora®) using the proposed route of administration, the clinical development program has been modest, consisting of two major studies and one additional small study in patients with mucositis.

Evidence for the efficacy of BEMA Fentanyl comes from a single efficacy study, FEN-201. The data from FEN-201 are supported by supplementary open-label data from studies FEN-113 and FEN-202. FEN-113 was a clinical pharmacology study with secondary endpoints assessing efficacy in mucositis pain, and FEN-202 was an open-label safety study with secondary endpoints that assessed efficacy.

FEN-201 was a double-blind, randomized, placebo-controlled, multiple crossover, multi-center study, conducted at 30 sites in the United States. It consisted of a titration phase, during which the subjects were titrated to an effective dose of BEMA Fentanyl, and a double-blind phase, which compared BEMA Fentanyl to placebo for the treatment of cancer BTP.

A total of 152 subjects were enrolled from 30 sites and 151 received study drug in the Titration Period. A total of 69 subjects (45.4%) discontinued during the Titration Period. Eighty-two subjects entered the Double-blind Period of the study and 80 subjects provided pain assessment within the 30-minute post-dose interval (intent-to-treat population; ITT).

FEN-202 was an open-label study to evaluate the safety and tolerability of BEMA Fentanyl. Two groups of subjects were eligible for enrollment; those who entered following successful completion of Study FEN-201, and those who were enrolled directly. A total of 236 subjects were enrolled in the trial according to the 120-day safety update.

The clinical safety of BEMA Fentanyl was established in three studies of subjects with cancer: a pharmacokinetic study of subjects with and without mucositis (FEN-113, 14 subjects), a double-blind crossover efficacy study in cancer subjects with breakthrough pain (FEN-201, 145 subjects), and a long-term safety in cancer subjects with breakthrough pain (FEN-202, 236 subjects) resulting in a total of 300 opioid-tolerant cancer patients exposed to at least one dose of study drug in studies FEN-201 and FEN-202. Eighty-one patients who enrolled in FEN-202 had previously participated in FEN-201. Subjects in FEN-113 were not required to be opioid tolerant.

Of the 300 opioid-tolerant cancer patients exposed to study drug, 122 were treated for at least 60 days, and 98 for at least 90 days. Forty-five patients were treated for 180-364 days, and 22 for at least a year.

Approximately 75,000 doses of BEMA Fentanyl in the dose range of 200 to 2400 μg were administered.

There is no post-marketing data to assess since BEMA Fentanyl is not currently marketed anywhere in the world.

1.3.2 Efficacy

Evidence for the efficacy of BEMA Fentanyl comes from a single Phase 3 study, FEN-201; A Double-Blind, Placebo-Controlled Evaluation of the Efficacy, Safety, and Tolerability of BEMA Fentanyl in the Treatment of BTP In Cancer Subjects.

The study population was comprised of cancer patients being treated for chronic pain with around-the-clock opioids and experiencing one to four breakthrough pain episodes per day. The study consisted of an open-label titration phase where patients determined an effective dose of study drug, and a double-blind phase during which patients were treated for nine episodes of breakthrough pain (six with study drug, three with placebo). Placebo doses were to have been randomly distributed over the double-blind period with one placebo dose included among every three doses, and at least one active dose between two placebo doses. With each episode of breakthrough pain, patients were to have taken the next dose in the prespecified sequence, and record pain intensity and perceived pain relief at specified intervals after each dose of study drug. The use of rescue medication was to have been recorded.

The primary efficacy endpoint was the summed pain intensity difference 30 minutes after dosing (SPID 30). The SPID was calculated as a weighted sum of the pain intensity differences (PID) of all time points at or before the time point of interest. There were multiple secondary

endpoints including SPID at other time points, pain relief, pain intensity difference, total pain relief, and global performance.

Overall, the design of study FEN-201, the population, and the primary endpoint are acceptable. The Division considered submission of a single adequate and well-controlled efficacy study in the context of previous Agency findings for fentanyl acceptable for this NDA. Although the duration of the controlled portion of the study was short, this is considered an adequate evaluation for efficacy for this type of product in a cancer population, particularly as dosing can be adjusted as needed.

The results of study FEN-201 support the efficacy of BEMA Fentanyl for the management of BTP in patients with cancer who are on around-the-clock opioids for chronic pain and are opioid tolerant. Both the Applicant's analysis of the primary endpoint and that of the Agency's statistical reviewer (Dr. Joan Buenconsejo) showed there was a statistically significant difference ($p < 0.05$) between BEMA Fentanyl and placebo for the SPID30. The SPID30 (LS mean ± SE) was 47.9 ± 3.87 for BEMA Fentanyl and 38.1 ± 4.30 for placebo. The difference in LS mean SPIDs between BEMA Fentanyl and placebo was 9.74 (95% CI: 3.31, 16.18).

Although several secondary endpoints were studied and analyzed, the Applicant did not apply a multiplicity adjustment, and they are therefore considered exploratory. However, the results of the analyses of the secondary endpoints are supportive of the primary endpoint and the finding of efficacy for BEMA Fentanyl compared to placebo.

The SPID values for BEMA Fentanyl differ significantly from placebo starting with SPID15, however the onset of action of BEMA Fentanyl cannot be accurately determined from this information. Pain relief was not assessed during the trial using the double stop-watch method (measuring time to "perceptible" pain relief and "meaningful" pain relief), so that the true onset of action of the drug was not measured during Study FEN-201, and no claims may be made regarding time to onset of pain relief.

The efficacy findings for BEMA Fentanyl appear consistent with those for Fentora and Actiq, however there are important differences in bioavailability between the three products that are the source of potential safety concerns.

1.3.3 Safety

The clinical safety of BEMA Fentanyl was established in three studies of subjects with cancer: a pharmacokinetic study of subjects with and without mucositis (study FEN-113, 14 subjects); a double-blind crossover efficacy study in opioid-tolerant cancer subjects with breakthrough pain (FEN-201, 145 subjects); and a long-term safety study in cancer subjects with breakthrough pain (FEN-202, 236 subjects).

The safety database submitted by the Applicant in the120-day safety update was comprised of 300 opioid-tolerant cancer patients exposed to at least one dose of study drug (Subjects from FEN-113 were analyzed separately). Of these, 122 were treated for at least 60 days, and 98 for