



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
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Addendum to Clinical Review
NDA 22-266

DATE: July 21, 2008

REVIEWER Ellen Fields, M.D., M.P.H.

DRUG: Onsolis (Fentanyl Buccal Soluble Film)

This is an addendum to the primary clinical review of NDA 22-266, which was completed on June 6, 2008.

Change in Recommendation for Regulatory Action

The recommendation for regulatory action for Onsolis in the original NDA review was "approval". I am changing the recommendation to "approvable" based on the current requirement that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for the approval of this product. Although a Risk Management Plan was submitted with the original NDA, it was found insufficient to meet the requirements of the recent amendment to the FDCA.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA determines 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. The Agency has determined that a REMS is necessary for Onsolis to ensure that the benefits of the drug outweigh the risks of: 1) use in non-opioid-tolerant individuals; 2) abuse and misuse; and 3) unintended (accidental) exposure.

Errors in Original NDA Submission

On June 27, 2008 the Applicant notified the Division that Table 12 in the FEN-201 clinical study report body contained errors. Due to transcription errors, the data presented as SPID 5 minutes is actually SPID 10 minute data and the data presented as SPID 10 minutes is actually PID 10 minute data. The Applicant noted that the project

statisticians and data managers confirmed that the SAS source tables and datasets are correct. In addition, the Applicant confirmed that the primary endpoint SPID 30 minute data in Study Report Body Table 11 is accurate and that the secondary endpoint SPID 15, 45, and 60 minute data in Study Report Body Table 12 are accurate.

The corrected values have been double-checked by Dr. Joan Buenoconsejo (statistical reviewer), and they are correct. These errors do not impact the finding of efficacy for the study drug or the proposed prescribing information.

The original and corrected tables are shown below:

FEN-201 Original Clinical Study Report

Table 12 Sum of Pain Intensity Difference by Time Point: ITT Population

SPID^b	Placebo (n = 77)	BEMATM Fentanyl^a (n = 79)
5 Minutes		
Number of episodes	176	361
Mean (SEM)	5.0 (0.63)	5.7 (0.49)
SD	8.54	9.60
Median	0.0	0.0
Minimum, Maximum	-10, 50	-15, 80
P value ^c	0.179	
10 Minutes		
Number of episodes	184	379
Mean (SEM)	0.7 (0.08)	0.8 (0.07)
SD	1.07	1.28
Median	0.0	0.0
Minimum, Maximum	-1, 5	-3, 8
P value ^c	0.458	

Corrected July 3, 2008 (changes are in red)

Table 12 Sum of Pain Intensity Difference by Time Point: ITT Population

SPID^b	Placebo (n = 77)	BEMATM Fentanyl^a (n = 79)
5 Minutes		
Number of episodes	176	361
Mean (SEM)	1.5 (0.29)	1.6 (0.21)
SD	3.83	3.90
Median	0.0	0.0
Minimum, Maximum	-5, 25	-5, 40
P value ^c	0.440	
10 Minutes		

Table 12 Sum of Pain Intensity Difference by Time Point: ITT Population

SPID^b	Placebo (n = 77)	BEMATTM Fentanyl^a (n = 79)
Number of episodes	184	379
Mean (SEM)	5.0 (0.63)	5.7 (0.49)
SD	8.54	9.60
Median	0.0	0.0
Minimum, Maximum	-10, 50	-15, 80
P value ^c	0.179	

As a result of the discovery of the errors in Table 12, the Applicant assessed the original submission for additional problems. They found the following (submitted July 3, 2008):

1. CTD Section 2.7.3: Table 8 (Summary of All Efficacy Outcome Measures) present least-squares (LS) mean SPID values, but should have presented mean SPID values.
2. CTD Section 2.5: Table 13 (FEN-201: Summary of All Efficacy Outcome Measures) presented least-squares (LS) mean SPID 30 minute values but should have been mean SPID 30 minute values.
3. FEN-201 Clinical Study Report Table 28 (Treatment-Related Adverse Events during the Titration and Double-Blind Periods: Safety Population): A single incidence of retching was not presented in the table. The SAS source tables and datasets were correct. The tables in the ISS correctly presented this case of retching.
4. CTD Section 2.5: Due to a transcription error, the incidence of vomiting in short-term administration was presented as 20.6% rather than 6.6% in the Adverse Event section on page 35. The number (%) of subjects experiencing vomiting was 20 (6.6%). BDSI can confirm that the correct incidence number and percentage were presented the Integrated Summary of Safety.

There was no impact from the errors noted above on the safety or efficacy conclusions for study FEN-201 or for Onsolis overall.

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/s/

Ellen Fields
7/21/2008 11:48:56 AM
MEDICAL OFFICER



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 17, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Silvia Calderon, Ph.D., Team Leader
Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Lori A. Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: NDA-22-266 BEMA Fentanyl (established name: fentanyl buccal soluble film,; trade name: Onsolis)
Indication: Management of breakthrough pain in opioid-tolerant cancer patients
Dosages: 200, 400, 600, 800, and 1200µg, buccal administration
Company: BioDelivery Sciences International (BDSI)

Materials received: NDA in Electronic Document Room

This memorandum responds to a consultation from the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), concerning the risks of Onsolis. CSS has reviewed the pertinent sections of the NDA including clinical pharmacology and safety, chemistry, product formulation, and clinical trial databases. In addition, CSS is collaborating with the review division on the development of REMS for Onsolis.

I. Background

BioDelivery Sciences International (BDSI) has filed this 505(b)(2) New Drug Application (NDA) in support of registration of BEMA Fentanyl (tradename: Onsolis) for the treatment of breakthrough-pain (BTP) in opioid tolerant cancer patients with chronic pain. The reference drugs for this 505(b)(2) submission are NDA 20-747 Actiq™ and NDA 19-813 Duragesic®.

NDA 22-266 proposes five film strengths (200, 400, 600, 800 and 1200 µg) for buccal mucosal administration of fentanyl, one of the most potent μ opioid agonists (Gutstein and Akil in Goodman & Gilman, 11th Ed., 2006). The product is indicated for the management of breakthrough pain in patients with cancer pain who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain. Onsolis is a highly

concentrated, high-dose, highly bioavailable, rapid onset fentanyl product that will be used in an unsupervised patient setting.

Because of its high potential for abuse, fentanyl is controlled in Schedule II of the Controlled Substances Act (CSA) (21 U.S.C. 812), as are similar opiates approved for medical use, including hydromorphone, morphine, and oxycodone.

II. Recommendations

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.

CSS has attended meetings on the product label, product insert, and other safety related issues, and continues to work with DAARP and others on the development of an appropriate REMS for Onsolis.

III. Summary

A. Product description and pharmacology

As described by the applicant, the drug product Onsolis (fentanyl buccal soluble film) is a flat bilayer rectangle with round corners, pink on one side and white on the other side [see figure below]. The pink mucoadhesive layer contains the drug substance, fentanyl citrate, and the white backing layer controls the erosion rate and residence time of the dosage form in the mouth. The white backing layer does not contain drug product, and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The drug product is designed to provide drug release through the buccal mucosa when the pink side of the unit is placed on the mucosa. The unit is designed to erode over a period of approximately 30 minutes.



Onsolis drug product schematic (lateral view)

b(4)

The drug product is available in five strengths: 200, 400, 600, 800, and 1200 µg fentanyl free base per unit. After titration to the appropriate dose, the daily dose is no more than four units/day (or a maximum of 4800 µg maximum/day). Each unit is packaged in a child-resistant ~~plastic~~ foil.

b(4)

Following buccal application, active pharmaceutical ingredient from Onsolis is rapidly absorbed, and the absolute bioavailability is 71%. Approximately 51% of the total dose of Onsolis is absorbed from the buccal mucosa and about 20% is swallowed with saliva and slowly absorbed from the GI tract.

Onsolis' apparent elimination $T_{1/2}$ is 8 – 15 hr. Onsolis exhibits a linear PK over 200 – 1200 μg doses, and no fentanyl PK changes were noted due to pH changes, external heat application or in mucositis. PK parameters of Onsolis compared to Actiq are shown in the Table 1, below. Pharmacokinetic characteristics of Onsolis that increase its risks compared to Actiq include its higher bioavailability (71% vs 47%), shorter T_{max} , and greater C_{max} (67%) and AUC (41%).

Table 1
Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Receiving Single Doses of ONSOLIS or Actiq

Pharmacokinetic Parameter	ONSOLIS (800 μg)	Actiq (800 μg)
C_{max} (ng/mL)	1.67 \pm 0.75	1.03 \pm 0.25
AUC _{inf} (hr·ng/mL)	14.46 \pm 5.4	10.30 \pm 3.8
T_{first} (min)	9.0 \pm 4.8	13.2 \pm 10.8
T_{max} (hr)	1.00 (0.75 – 4.00)	2.00 (0.50 – 4.00)

* Data for T_{max} presented as median (range); other data are presented as mean \pm SD

[source: Proposed label for BEMA Fentanyl]

B. Safety of Onsolis¹

Safety data summary:

The safety database for Onsolis comprised subjects from three studies:

- FEN-201: Phase 3 efficacy and safety [pivotal study]
- FEN-202: open-label safety
- FEN-113: PK study in patients with mucositis (analyzed separately)

FEN-201 was randomized, double-blind, placebo-controlled, multiple crossover study in which efficacy, safety and tolerability of Onsolis were evaluated in the treatment of breakthrough pain in cancer subjects. The sponsor met their primary outcome measures for efficacy in this trial.

Although 67 study deaths occurred in the cancer population used in these trials, no deaths were definitively related to study drug. Likewise, the most common serious adverse events were infections (13%) and neoplasm/disease progression (16%). The clinical status of the patients and their concomitant medications made assessment of causality difficult. One subject experienced urinary retention that was rated as “possibly related” to study drug. This occurred in a setting of increased doses of background opiates. This is the only SAE that was assessed by a study investigator as being related to Onsolis.

¹ A primary review of the sponsor's database for safety was not performed. Rather this review relied on the review of Ellen Fields, M.D., M.P.H, dated June 6, 2006, as well as information in the sponsor's Summary of Clinical Safety and Safety Updates.

Abuse, misuse and diversion data summary

According to the sponsor, there were no reports of overdose. A number of subjects were noted to have stopped the study without returning the study drug. This included cases where the study subject died [subjects 004-1002, 031-1002, 032-1002, 038-2001, 052-2017] or experienced adverse events [004-1024, 018-1012, 018-1014]. Other cases in which the study drug was not returned include those: where the study drug was withdrawn due to noncompliance [015-1001, 052-2020], where study participation was stopped due to consent withdrawal [018-1001, 018-1003, 043-2006] or in which subjects were lost to follow up [032-2005]. In addition, subject 023-1004 did not return the study drug at one of the follow up visits; it was noted that the subject's daughter had used the study drug, without apparent adverse effects. This subject was counseled on the need for greater security, but was continued in the study. These cases indicate the need for better drug accountability and security measures to assure safety in the postmarketing period.

The sponsor did not perform additional studies to assess the abuse potential of fentanyl in the BEMA delivery system.

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/s/

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7/17/2008 03:01:12 PM
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