Appendix 1

Division Memo and Cross-Discipline Team Leader Review

Date	August 4, 2008
From	Sharon Hertz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-266 505(b)(2)
Applicant	BioDelivery Sciences, International
Date of Submission	October 31, 2007
PDUFA Goal Date	August 29, 2008
Proprietary Name / Established (USAN) names	Onsolis/Fentanyl buccal soluble film
Dosage forms / Strength	200, 400, 600, 800, and 1200 mcg
Proposed Indication(s)	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
Recommended:	Approvable - Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Ellen Fields, M.D.
Statistical Review	Joan Buenconsejo, Ph.D.
Pharmacology Toxicology Review	Gary Bond, Ph.D.
CMC Review	Xavier, Ysern, Ph.D.
Microbiology Review	NA
Clinical Pharmacology Review	David Lee, Ph.D.
DDMAC	Michelle Safarik, P.A.-C.
DSI	Sherbet Samuels, R.N., M.P.H.
OSE/DMETS	Kristina Arnwine, Pharm.D.
OSE/DRISK	Jeanine Best, MS.N., R.N., P.N.P,
Controlled Substances Staff	Lori Love, M.D., Ph.D.

1. Introduction and Background

This is a 505(b)(2) application for fentanyl buccal soluble film, a small bioerodible film that adheres to the buccal membrane. The listed drug referenced by this application is Actiq (NDA 20-747). For this reformulation of fentanyl, one clinical study and several pharmacokinetic studies were submitted in support of this application. During development the product had been referred to as BEMA Fentanyl and this will be continued in this review.

This application represents the third NDA for an oral transmucosal fentanyl formulation. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due the similarity in appearance to a lollipop. A RiskMAP was created to attempt to manage some of the risk associated with this product. In addition to identifying the risk for accidental pediatric exposure and providing some methods to try and minimize that risk, other goals described in the RiskMAP include preventing use in opioid non-tolerant patients and other off-label use. The only clearly unique adverse event associated with Actiq in postmarketing experience has been the occurrence of dental caries, related to the sugar content in the Actiq lozenge.

Fentora was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. The only adverse event associated with Fentora that has differed from Actiq in pre and postmarketing experience has been the occurrence of local ulcers in the mouth at the site of drug exposure. Fentora was approved with a RiskMAP comparable to Actiq. Actiq and Fentora were approved for the same indication sought by the applicant, 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 intended population is already on around-the-clock opioids for pain and has episodes of pain that stand out from background pain. This indication reflects the need for a specific treatment to meet the needs of cancer patients with breakthrough pain, characterized by a relatively early onset of action, relatively short duration of action and high analgesic potency. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patients to be opioid tolerant, a physiological state in which patients are more tolerant to the CNS depression and respiratory depression associated with opioids.

Based on the postmarketing history of Actiq, it has become clear that prescribers have found Actiq to be useful in patients without cancer pain, both in the setting of chronic pain with episodes of breakthrough pain and other painful conditions. Of note, use of the term breakthrough pain in noncancer pain is somewhat controversial. In the Actiq RiskMAP quarterly reports, the use of Actiq in noncancer pain has exceeded its use in cancer pain, although it is used primarily in opioid tolerant patients with chronic noncancer pain.

Fentora has greater bioavailability than Actiq and the formulation is less easily removed from the mouth once dosing has begun. Efforts were made to make the difference in bioavailability clear in the Fentora labeling with specific statements that patients should not be converted from Actiq on a mcg for mcg basis and that Fentora is not a generic version of Actiq. However, postmarketing reports have demonstrated a variety of medication errors that include direct conversion on a mcg for mcg basis by prescribers and product substitution at the pharmacy level, in addition to incorrect dosing instructions. The quarterly RiskMAP reports document the very disturbing trend of steadily increasing frequency of use in patients who are not opioid tolerant. In the first year of marketing there have been deaths reported in two patients prescribed Fentora for headache.

As a result of the postmarketing information from Actiq and Fentora, it appears that the RiskMAP in place for Actiq and Fentora is not effective in mitigating the risks of these products. During a joint meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees on May 6, 2008, the committee members heard presentations from the FDA, SAMHSA and Cephalon about the risks associated with Fentora and the failure of the RiskMAP to mitigate those risks. The committee recommended a more comprehensive program that included patient and physician registration and improved risk communication.

2. CMC/Device

Dr. Xavier Ysern conducted the CMC review and sections of his review may be included in this memo. The drug substance, fentanyl citrate, is manufactured by ——— and the applicant has referenced DMF ——— Agency review of this DMF has found it to be adequate. The drug substance specifications, including purity, have also been found to be adequate. b(4)

The drug product is a flexible flat, bilayer film. The backing layer is white, ——— The mucoadhesive layer is pink ——— The basic film is the same for all strengths, 200, 400, 600, 800, and 1200 mcg, which differ only by surface area. The film is ——— and each unit is packaged in a child-resistant foil pouch. There are no novel excipients. The drug product specifications, including content uniformity, were found to be adequate and conform to ICH guidances. Adequate stability data was provided to assign a shelf-life of 24 months. b(4)

The facilities review and inspection were found to be acceptable.

3. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was performed by Dr. Gary Bond and sections of his review may be included in this memo. The applicant has referenced the Agency's prior finding of safety and efficacy of Actiq in lieu of performing most of the nonclinical studies that would have been required. Studies that were required to be performed by the applicant to support this application were a 28-day buccal toxicity study in dogs and two local tolerance studies in dogs. The applicant also provided a summary of primary and secondary pharmacodynamic studies, a safety pharmacology study and pharmacodynamic drug interaction study, but these were not reviewed for this application.

The 28-day, repeat-dose toxicity study of fentanyl citrate and the local tolerance studies in dogs demonstrated decreased activity, excessive salivation, brown mucous in feces, abnormal gait and stance, emesis, and tremors. These findings were related to the known pharmacological activity of fentanyl with no newly identified systemic or local adverse effects.

Although Dr. Bonds' review states that the proposed label is based on the labels for NDA 20-747 (Actiq) and NDA 19-813 (Duragesic), as noted in the memo by Dr. Wasserman, the labeling for BEMA Fentanyl is complete using references to Actiq alone.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology and biopharmaceutics review was conducted by Dr. David Lee and sections of his review may be included in this memo. Fentanyl is metabolized in the liver and intestinal mucosa by CYP3A4. There is a significant first pass effect. Less than 7% of the dose is excreted unchanged in the urine and even less in the feces. While there is no established dissolution testing for this type of dosage form, dissolution testing was performed and found that dissolution is essentially complete in 30 minutes under the conditions studied.

Six clinical pharmacology studies were submitted and reviewed in support of this application as presented in the following table modified from Dr. Lee's review. Studies of normal volunteers utilized naltrexone blockade to prevent opioid-related effects.

Table 1 Clinical Studies

Study	Title	Formulation
FEN-107	A comparison of the pharmacokinetics of three different formulations of BEMA Fentanyl with Actiq®	1, 2, 3
FEN-109	An evaluation of adherence and fentanyl absorption from BEMA™ discs under a range of conditions	1
FEN-110	An evaluation of the single-dose pharmacokinetics of BEMA™ fentanyl	1
FEN-112	An evaluation of the multiple-dose pharmacokinetics of BEMA in normal healthy volunteers	1
FEN-113	An evaluation of fentanyl absorption from the BEMA™ delivery system in the presence of mucositis	1
FEN-114	An evaluation of absolute bioavailability and transmucosal absorption of fentanyl from the BEMA™ delivery system	1
FEN-201	A double-blind, placebo controlled evaluation of the efficacy, safety and tolerability of BEMA™ fentanyl in the treatment of breakthrough pain in cancer subjects	1
FEN-202	An open-label, long-term treatment evaluation of the safety of BEMA™ fentanyl use for breakthrough pain in cancer subjects on chronic opioid therapy	1

F: Formulation 1- pH 7.25; 2 – pH 6.0; 3 – pH 8.5

BEMA Fentanyl adheres to the mucosal surface allowing for direct contact with the mucosa. The fentanyl layer dissolves in saliva. The film is manufactured [redacted] b(4) The absolute bioavailability of fentanyl from BEMA Fentanyl was 71% (FEN-114) as demonstrated in the following table from Dr. Lee's review. This table also demonstrates the equivalence across dosage forms as the single 800 mcg unit was comparable to four simultaneous 200 mcg units.

Table 2 Results of Study FEN-114

Parameter	Treatment A: 200 mcg IV Fentanyl Citrate				Treatment B: 800 mcg Oral Fentanyl Citrate			
	n	Mean	SD	CV%	n	Mean	SD	CV%
Tmax (hr) a	12	**0.17 (0.08 – 0.37)**			12	**3.00 (1.00 – 4.00)**		
Cmax (ng/mL)	12	1.46	0.656	44.97	12	0.694	0.210	30.21
AUCinf (hr·ng/mL)	12	4.620	1.513	32.76	12	6.385	2.275	35.63
T1/2 (hr)	12	18.03	10.08	55.91	12	13.26	5.68	42.80
	Treatment C: 1 × 800 mcg BEMA Fentanyl				Treatment D: 4 × 200 mcg BEMA Fentanyl			
Parameter	N	Mean	SD	CV%	n	Mean	SD	CV%
Tmax (hr) a	12	**1.50 (0.75 – 4.00)**			12	**2.50 (1.00 – 4.00)**		
Cmax (ng/mL)	12	1.33	0.307	23.01	12	1.33	0.429	32.30
AUCinf (hr·ng/mL)	12	13.03	3.452	26.50	12	13.09	3.616	27.62
T1/2 (hr)	12	19.03	8.31	43.67	12	18.29	4.14	22.61
Last time point: 48 hours								
Comparison of AUCinf values following buccal and oral administration indicated that								

Approximately 51% of the administered dose is absorbed across the buccal mucosa, the remainder is swallowed. In comparison, the absolute bioavailability of an Actiq dose is 47%. In Study FEN-107 where the two products were compared, the Cmax of fentanyl from a dose of BEMA Fentanyl was 62% higher than a comparable dose of Actiq and the AUC was 40% higher for BEMA Fentanyl as shown in the **following table from Dr. Lee's review.**

Table 3 Results of Study FEN-107

Pharmacokinetic Parameter	BEMA Fentanyl pH 7.25 (800 mcg)	Actiq (800 mcg)
Cmax (ng/mL)	1.67 ± 0.75	1.03 ± 0.25
AUCinf (hr·ng/mL)	14.46 ± 5.4	10.30 ± 3.8

The Cmax and AUC of BEMA Fentanyl were dose-linear from 200 mcg through 1200 mcg as represented in the within-study data (FEN-110) in the following **table taken from Dr. Lee's** review. The half-life also increased with increasing dose suggesting possible depot formation with the higher doses.

Table 4 PK data from Study FEN-110

Pharmacokinetic Parameter (Mean ± SD)	BEMA 200 mcg	BEMA 600 mcg	BEMA 1200 mcg
Cmax (ng/mL)	0.38 ± 0.07	1.16 ± 0.19	2.19 ± 0.54
AUCinf (hr·ng/mL)	3.46 ± 0.72	11.72 ± 5.29	20.43 ± 4.52
Tmax (hr) [Median (range)]	**2.00 (1.00 – 4.00)**	**2.00 (1.00 – 4.00)**	**3.00 (0.75 – 4.00)**
T1/2 (hr)	8.15 ± 1.8	14.49 ± 8.40	13.60 ± 4.81

The applicant assessed the effects of heat on the PK of BEMA Fentanyl by applying a heating pad to the cheek and following exposure to a hot beverage. There was no clinically relevant effect from heat. No exposure-response relationship analysis was performed by the applicant. There was no formal multiple-dose study. In Study FEN-112, a 600 mcg BEMA Fentanyl was dosed hourly for three doses and displayed PK characteristics consistent with a single 1800 mcg dose.

There were no clinically relevant gender differences. Pediatric studies were not submitted with this application. There were no studies conducted to specifically assess the effects of advanced age. There were elderly subjects enrolled in the efficacy study and no clinically notable differences were observed with respect to safety or efficacy.

Neither the effects of hepatic impairment nor renal impairment on the PK of BEMA Fentanyl were studied. Based on the known metabolic pathway utilizing CYP3A4, consideration must be given to whether BEMA Fentanyl can be used safely in severe hepatic impairment and these patients need to be watched very closely during titration. Given the greater bioavailability of BEMA Fentanyl compared to Actiq, Actiq might be a more suitable product for use in patients with hepatic impairment. It is less clear that renal impairment would have a substantial impact on the PK of fentanyl itself, and the major metabolite, norfentanyl, is not active.

Study FEN-113 examined the effect of Grade 1 mucositis on the bioavailability of fentanyl from BEMA Fentanyl. No clinically relevant differences were found.

Drug-drug interaction studies were not conducted.

5. Clinical Microbiology

NA

6. Clinical/Statistical- Efficacy

Dr. Ellen Fields conducted the clinical review of efficacy and Dr. Joan Buenconsejo conducted the statistical review. Sections of their reviews may be included in this review. One clinical study was submitted in support of efficacy for this 505(b)(2) application and is reviewed in detail by Dr. Fields. This was a double-blind, placebo-controlled, 9-period crossover study. Patients with breakthrough pain from cancer, receiving around-the-clock opioids for background pain, with from one to four episodes of breakthrough pain per day were eligible for enrollment. Patients were titrated to an effective and tolerable dose over a two-week period, defined as the dose capable of providing adequate pain relief of a breakthrough pain episode with one dose. Patients were then sent home with nine doses of study drug in randomized order and instructed to use the doses in sequence. Six of the doses were active

drug and three were placebo. Patients were to record their pain intensity before and at 5, 10, 15, 30, 45, and 60 minutes following each dose of study drug using an electronic diary. Patients were permitted to use their previous rescue medication if adequate pain relief had not occurred by 30 minutes after study drug. This is the same basic study design used for the Actiq and Fentora efficacy studies.

One hundred fifty-two patients were enrolled and 151 began titration. Eighty-two patients completed the titration period and entered the double-blind period. Lack of efficacy and adverse event accounted for only 15 of the patients who failed titration according to the applicant, but in the following table, Dr. Fields reevaluated the reasons for failed titration and found an additional seven patients with adverse events from among the cases reported as consent withdrawn or other.

Table 5 Reason for Discontinuation During Titration, FEN-201

Reason for Discontinuation During Titration	**Adjudicated by Applicant**	**Adjudicated by Reviewer**
	# (%) N=151	
Consent Withdrawn	22 (14.5)	4 (2.6)
Other	11 (7.2)	5 (3.3)
Adverse Event	10 (6.6)	17 (11.2)
Noncompliance with e-diary	8 (5.3)	12 (7.9)
Lack of Efficacy	5 (3.3)	5 (3.3)
Not Rx'ing 1 episode/day	5 (3.3)	5 (3.3)
Noncompliance with admin	3 (2.0)	7 (4.6)
Did not use any study drug	-	3 (2.0)
Death	3 (2.0)	3 (2.0)
Protocol Deviation	2 (1.3)	4 (2.6)
Completed titration but didn't enter DB	1 (0.6)	4 (2.6)
Lost to follow-up	0	0
Total	69	69

Eighty-one of the 82 subjects received double-blind study medication and were included in the ITT population, one patient failed to record any pain assessment with the first 30 minutes post dose. Twelve subjects discontinued early during the double-blind period due to a variety of reasons described by Dr. Fields.

The patients who were successfully titrated found effective and tolerable doses across the spectrum of available strengths as shown below **in the table from Dr. Fields' review.**

Table 6 Doses Used in Double-Blind Study

BEMA strength (μg)	Double-blind phase N=81 n (%)
200	4 (4.9)
400	15 (18.5)
600	23 (28.3)
800	19 (23.4)
1200	20 (24.6)

The primary efficacy endpoint was a comparison of the summed pain intensity difference at 30 minutes (SPID30) following active or placebo treatments for the intent-to-treat population. Missing data were imputed using last observation carried forward. For subjects who used rescue, the last score prior to rescue was imputed to the remaining time points. There was a statistically significant difference in the SPID30 between the treatment groups favoring the BEMA Fentanyl over placebo. Dr. Buenconsejo performed a reanalysis of the data and additional sensitivity analyses and confirmed the findings. The SPID results are shown in the following figure. The applicant did not plan any correction for multiplicity of the p-values at the secondary time points after thirty minutes and these were to be considered exploratory endpoints. The applicant applied a closed, sequential step down procedure for the time points earlier than 30 minutes. Of the earlier time points, only the 15 minute SPID reached statistical significance.