CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-266

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-266	Submission Date: 10/28/07
Submission Type; Code:	505(b)(2); 3S
Brand/Code Name:	**Onsolis™ (fentanyl buccal soluble film)**
Generic Name:	[redacted] b(4)
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Anesthesia, Analgesia, and Rheumatology Products
Sponsor:	BioDelivery Sciences International, Inc.
Relevant IND(s):	62,864
Formulation; Strength(s):	200, 400, 600, 800, 1200 µg
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
Proposed Dosage Regimen:	• Initial dose of Onsolis: 200 mcg • Individually titrate to a dose that provides adequate analgesia without undue side effects using a single Onsolis unit per breakthrough cancer pain episode • Once a successful dose is determined, limit usage of Onsolis to four or fewer episodes per day, which must be separated by at least 2 hours • Onsolis should only be used once per episode

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology Evaluation II **(OCP/DCP-II) has reviewed the Onsolis™ NDA 22-266 submitted on 4/9/07.**

From OCP perspective, the information contained in the Application is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the **Labeling for Onsolis™.**

1.2 Phase IV Commitments

None

1.3 Summary of CPB Findings

BioDelivery Sciences International, **Inc., has submitted Onsolis™ NDA 22-266 in** accordance with 505(b)(2) of the Food, Drug and Cosmetic Act for the use of Onsolis 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. Onsolis is a bioerodible mucoadhesive system which delivers fentanyl across the buccal mucosa. It is a flexible, flat, bilayer rectangle with round corners, pink on one side and white on the other side. The pink mucoadhesive side containing fentanyl adheres upon contact with the moist buccal mucosa. The white backing layer does not contain drug substance and it minimizes drug release into the oral cavity maximizing transmucosal diffusion. The dose unit dissolves within 15 to 30 minutes. Onsolis is available in five dose strengths: 200, 400, 600, 800, and 1200 µg fentanyl free base per unit. The concentration of drug

substance within the mucoadhesive layer is the same for all product strengths. The fentanyl dose is determined by the dose unit size, defined by surface area.

Applicant is relying on the Agency's previous findings of safety and efficacy for NDA 20-747 ([ACTIQ], oral transmucosal fentanyl citrate) approved in November of 1998 for the same indication. In addition, Fentora (fentanyl citrate buccal citrate) was approved for the same indication in September of 2006. There were a total of 7 clinical pharmacology studies submitted. One was a pilot study and used a developmental formulation but the remaining six studies used the final formulation. These studies established the pharmacokinetics of single and multiple doses, with and without oral mucositis, with and without heat (i.e., external or hot liquid in the mouth), and in comparison to Actiq. Efficacy was studied in the single Phase 3 study FEN-201, a double-blind, multiple period, placebo-controlled, crossover study. Subjects underwent open-label titration to a tolerable, effective dose and then were randomized. Additional safety information was obtained in the open-label long-term study FEN-202.

The following table contains fentanyl Cmax, AUC0-inf and Tmax information from all pharmacokinetic studies:

Treatments	n	**Cmax** Mean (SD) ng/mL	**AUC 0-inf** Mean (SD) h·ng/mL	**Tmax** Median (Range) h
Fentanyl 200 µg IV	**12**	**1.46 (0.66)**	**4.62 (1.5)**	**0.17 (0.08–0.37)**
Fentanyl 800 µg PO	**12**	**0.69 (0.21)**	**6.39 (2.28)**	**3.0 (1.0–4.0)**
Reference - Actiq 800 µg	**12**	**1.03 (0.25)**	**10.3 (3.8)**	**2 (0.5–4)**
BF 200 µg	**11**	**0.38 (0.08)**	**3.46 (0.72)**	**2 (1–4)**
BF 200 µg (patients with mucositis)	7	0.47 (0.32)	1.14 (0.71)[a]	**1 (0.45–3.92)**
BF 200 µg (patients without mucositis)	7	0.69 (0.54)	1.29 (0.87)[a]	**1 (0.5–1.5)**
BF 400 µg Without Heat	**6**	**0.68 (0.2)**	**4.43 (0.99)**	**2.0 (1–4)**
BF 400 µg Heating Pad	**6**	**0.6 (0.14)**	**4.1 (0.89)**	**2.0 (1–4)**
BF 400 µg Hot Tea	**6**	**0.54 (0.19)**	**3.51 (1.0)**	**2.0 (1–4)**
BF 600 µg	**12**	**1.16 (0.19)**	**11.72 (5.3)**	**2 (1–4)**
BF 600 µg	**12**	**1.08 (0.25)**	**9.1 (3.8)**	**1.0 (0.75–4)**
BF 600 µg	**12**	**1.01 (0.23)**	**9.6 (3.6)**	**2.0 (2–4)**
BF 600 µg x 3 doses (3 x Q1h)	**12**	**3.31 (0.81)**	**30.3 (10.4)**	**3.5 (3.25–3.75)**
BF 800 µg – pH 6	**12**	**1.4 (0.49)**	**13.7 (4.5)**	**2 (0.75–4)**
BF 800 µg – pH 7.25[b]	**12**	**1.67 (0.75)**	**14.46 (5.4)**	**1 (0.75–4)**
BF 800 µg – pH 8.5	**12**	**1.39 (0.41)**	**13.11 (4.8)**	**2 (0.5–4)**
BF 800 µg	**12**	**1.33 (0.31)**	**13.03 (3.45)**	**1.5 (0.75–4.0)**
BF 800 µg (4 x 200 µg units)	**12**	**1.33 (0.43)**	**13.09 (3.62)**	**2.5 (1.0–4.0)**
BF 1200 µg	**12**	**2.19 (0.54)**	**20.4 (4.5)**	**3 (2–4)**

a AUC is from 0-4 h interval
b Final pH

Exposure-response relationship

No exposure-response relationship was assessed in the Onsolis drug development program. Experience with Actiq was relied upon for the product development. In addition, clinical efficacy of Onsolis in treating episodes of breakthrough cancer pain was studied in the Phase 3 clinical study FEN-201 in opioid tolerant cancer subjects. The Applicant claims that Onsolis was more effective than placebo at reducing pain at the primary endpoint (sum of pain intensity differences at 30 minutes) as well as on most secondary endpoints. See Clinical review for final assessment of the efficacy of this product.

Linearity

The fentanyl Cmax and AUC values were dose-linear from 200 to 1200 μg (Study FEN-110).

Absolute bioavailability

The absolute bioavailability of fentanyl from Onsolis was approx. 71% (Study FEN-114). The absolute bioavailability of fentanyl administered as an oral solution was approx. 35%.

Comparison of AUCinf values following buccal and oral administration indicated that 51% of the administered Onsolis dose is absorbed via the buccal mucosa.

For the presently marketed ACTIQ formulation, the reported absolute bioavailability is approx. 47%. Since fentanyl exposure is greater from Onsolis, Onsolis should not be substituted for Actiq on a μg for μg basis.

Relative bioavailability

Compared to ACTIQ, Onsolis provided 62 and 40 % higher fentanyl Cmax and AUC, respectively. As stated above, Onsolis should not be substituted for ACTIQ on a μg for μg basis

Multiple dosing

Since the product will be used as needed when the patient experiences breakthrough pain episodes, there is no fixed dosing regimen. In one day, patients are advised not to use more than four units but these four units may be used as needed.

Gender
Overall, there were no appreciable differences in the Cmax and AUC values between males and females in this database.

Pediatric population

The Applicant requested a partial waiver for pediatric population [redacted] b(4)
On June 28, 2007 Agency issued a Written Request for pediatric studies in children aged 3 to 17 years old.

Effects of Heat Application

Heat application, either by heating pad to the external jaw or by hot liquid, did not increase fentanyl absorption from Onsolis applied to the buccal mucosa. The results of this study demonstrate that external heat application does not significantly increase drug delivery rate from Onsolis.

Assay

Fentanyl concentrations were measured with LC/MS/MS assay. Typically, quantitation was performed using weighted ($1/X_2$) linear least squares regression analyses generated from plasma calibration standards prepared immediately prior to each run. The assay procedure was found to be linear over the range of [redacted] b(4)
Precision and accuracy at the LLOQ were verified by analyzing at least two samples at the lowest standard concentration (0.0250 ng/mL) on each day of validation. The inter-day CV was 8.7% and the inter-day absolute deviation was 1.1%. The intra-day precision and accuracy at the LLOQ were verified by analyzing six samples at the lowest standard concentration during one day of validation. The intra-day CV was 4.8% and the intraday absolute deviation was 5.6%.

Overall, the information submitted in this NDA is acceptable pending a mutual agreement can be reached with the Applicant with respect to Onsolis Labeling. The Applicant is relying on the package insert of Actiq for all Clinical Pharmacology related language not obtained from pharmacokinetic studies conducted in support of this NDA.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the drug product?

Drug substance

Molecular Formula	$C_{22}H_{28}N_2O \cdot C_6H_8O_7$
Molecular Weight	Fentanyl citrate salt: 528.59 Fentanyl free base: 336.49
Dissociation Constants	The pK_a values of fentanyl are 7.3 and 8.4.
Solubility	The solubility is approximately 25 mg/mL in water at room temperature. The solution in water is clear and colorless.

Fentanyl citrate is soluble in methanol and sparingly soluble in chloroform.

Fentanyl citrate active pharmaceutical ingredient is manufactured by [redacted] b(4)

Drug product

BEMA Fentanyl is a bioerodible mucoadhesive system which delivers fentanyl across the buccal mucosa. The drug product is a flexible, flat, bilayer rectangle with round corners, pink on one side and white on the other side. The pink mucoadhesive side containing fentanyl citrate adheres upon contact with the moist buccal mucosa. The white backing layer does not contain drug substance and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The dose unit dissolves within 15 to 30 minutes.

The concentration of drug substance within the mucoadhesive layer is the same for all product strengths. The fentanyl dose is determined by the dose unit size, defined by the surface area. Each BEMA Fentanyl dose unit is debossed with a product strength identifier on the white backing side and packaged in a child-resistant [redacted] b(4) [redacted] foil, [redacted] package.

BEMA drug product schematic (lateral view):

[redacted]

b(4)

Dimensions:

Strength (µg)	Area (cm^2)	Weight (mg)	Length (mm)	Width (mm)	Thickness Mucoadhesive (mm)	Thickness Backing (mm)	Thickness Total (mm)
200							
400							
600							
800							
1200							

b(4)

b(4)

Drug product composition

Component	Amount (% w/w) for All Strengths[a]		Function	Quality Standard
	Mucoadhesive	Backing		
Fentanyl Citrate	[redacted]		Active	*USP*
Water				*USP*
Propylene Glycol				*USP*
Sodium Benzoate				*NF*
Methylparaben				*NF*
Propylparaben				*NF*
Ferric Oxide				*NF, JP*
Citric Acid				*USP*
Vitamin E				*USP*
Monobasic Sodium Phosphate				*USP*
Sodium Hydroxide				*NF*
Tribasic Sodium Phosphate				*NF*[c]
Polycarbophil				*USP*
Hydroxypropyl Cellulose				*NF*
Hydroxyethyl Cellulose				*NF*
Carboxymethylcellulose				*NF*
Titanium Dioxide				*USP*
Saccharin Sodium				*USP*
Peppermint Oil				*NF*
Total (%)	[redacted]		[redacted]	

b(4)

b(4)

b(4)

[a] = Expressed on a dry basis.
[b] = [redacted]
[c] = Purchased as [redacted] grade and tested to the *NF* monograph.
JP = *Japanese Pharmacopoeia.*
NF = *National Formulary.*

Unit composition (mg/unit):

Component	% wt/wt Dry Weight	Strength (µg Fentanyl Free Base)				
		200	400	600	800	1200
Fentanyl Citrate						
Water[a]						
Propylene Glycol						
Sodium Benzoate						
Methylparaben						
Propylparaben						
Ferric Oxide						
Citric Acid						
Vitamin E						
Monobasic Sodium Phosphate						
Sodium Hydroxide						
Tribasic Sodium Phosphate						
Polycarbophil						
Hydroxypropyl Cellulose						
Hydroxyethyl Cellulose						
Carboxymethylcellulose						
Titanium Dioxide						
Saccharin Sodium						
Peppermint Oil						
Total Weight (mg)						

[a] =

[b] =

b(4)

b(4)

b(4)

The commercial formulation is the same as that used in the Phase 3 clinical trials. The Phase 3 clinical formulation had the same excipients as the formulations used in all the Phase 1 studies, at the same concentrations. The exception is in Study FEN-07, where the formulation pH was adjusted to three different values to optimize the delivery.

Parameter	Actiq 800 µg			BEMA Fentanyl 800 µg pH 6			BEMA Fentanyl 800 µg pH 7.25			BEMA Fentanyl 800 µg pH 8.5		
	N=12			N=12			N=12			N=12		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
Tmax (hr) 1	2.0 (0.50 – 4.0)			2.0 (0.75 – 4.0)			1.0 (0.75 – 4.0)			2.0 (0.50 – 4.0)		
Cmax (ng/mL)	1.03	0.25	24.19	1.40	0.49	35.12	1.67	0.75	45.07	1.39	0.41	29.44
AUClast (hr·ng/mL)	9.044	3.53	39.01	12.17	4.28	35.19	12.99	5.59	43.03	11.82	4.54	38.37
AUCinf (hr·ng/mL)	10.30	3.84	37.29	13.68	4.55	33.24	14.46	5.40	37.36	13.11	4.77	36.40
T1/2 (hr)	15.33	6.85	44.67	15.12	5.09	33.66	14.36	2.89	20.13	13.33	4.14	31.04

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Drug development plan

Buccal drug delivery is dependent upon drug dissolving in saliva, the mucosal surface area, and the time of that contact. The surface area for buccal absorption is approximately 25 cm^2 per side of the mouth. The saliva, with a pH of approximately 7, is produced at a known rate of 0.04 mL/minute per side (non-stimulated). Fentanyl has a pKa of 8.4 and is most soluble at pH 6 or below.

Onsolis provides a fixed dose per unit surface area and insures mucosal contact and the prolonged contact time. With respect to fentanyl solubility, product is manufactured (in [redacted] steps) with buffering agents such that the desired pH of 7.25 is achieved and maintained at the mucosal adhesion site, when a dose unit is hydrated on contact with the saliva. b(4)

A total of 68 volunteers, 14 with cancer, in 6 studies, received at least one dose administration of the final formulation of BEMA Fentanyl and an adequate number of blood samples were taken to provide a sufficient number of data points for pharmacokinetic analysis. All studies involving normal volunteers, naltrexone was administered prior to fentanyl dose administration to prevent the pharmacodynamic effects of opiate administration.

Mechanism of action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Therapeutic Indications
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

2.1.3 What are the proposed dosage and route of administration?

Route of administration: