CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-266

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum

NDA NUMBER:	**22-266**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**10/31/2007**
PRODUCT:	
Trade Name:	**ONSOLIS™**
Established name:	**Fentanyl buccal soluble film**
INDICATION:	**Breakthrough cancer pain**
INTENDED CLINICAL POPULATION:	**Adult opioid-tolerant cancer patients receiving around-the-clock opioids with breakthrough pain**
SPONSOR:	**BioDelivery Sciences International**
DOCUMENTS REVIEWED:	**Primary Pharmacology/Toxicology review; prior Agency communications; eCTD where necessary**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Gary P. Bond, Ph.D., DABT**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Kimberly Compton, R. Ph.**

EXECUTIVE SUMMARY

I. BACKGROUND

NDA 22-266 pertains to ONSOLIS™, the established name being fentanyl buccal soluble film, which was submitted by BioDelivery Sciences International. During development, the product was under IND 62,864 and was referred to as BEMA™-fentanyl. ONSOLIS is a 2-layer film produced in strengths of 200, 400, 600, 800 and 1200 µg fentanyl free base which adheres when applied to the buccal mucosa. The buccal layer contains a matrix of bioerodible adhesive polymers combined with fentanyl citrate while the exterior layer is a bioerodible backing film designed to reduce fentanyl release into the oral cavity where it would otherwise be swallowed and largely eliminated by first-pass hepatic metabolism. The indication sought is for opioid-tolerant individuals with breakthrough cancer pain, an identical indication as found in Cephalon's ACTIQ® (fentanyl citrate) oral transmucosal lozenge [NDA 20-747, approved 1998], which is available in strengths up to 1600 µg fentanyl base and which serves as the reference listed drug (RLD) for this 505(b)(2) application. Another buccal fentanyl drug product recently approved, which does not serve as a RLD for the product likely for reasons of unexpired patents and/or exclusivity is FENTORA® (fentanyl buccal tablet) approved in 2006 [NDA 21-947] in strengths of up to 800 µg fentanyl base.

It is noted that an additional approved fentanyl product, Alza Corporation's DURAGESIC® (fentanyl transdermal system) [NDA 19-813], is described in the nonclinical sections of the NDA. Although DURAGESIC is described as a RLD in the primary review, this product is not listed as a RLD in the submitted NDA nor for that reason has patent/exclusivity certification been conducted. The Applicant's proposed label does not contain language found exclusively in the prescribing information for DURAGESIC though it is noted that significant nonclinical language is shared between DURAGESIC and ACTIQ product labels. Upon review of nonclinical sections of the eCTD, studies conducted in support of DURAGESIC which are not described in the approved label for ACTIQ includes specific genetic toxicology assays (Ames reverse bacterial mutation assay, Unscheduled DNA Synthesis assay in primary rat hepatocytes, BALB/c-3T3 transformation assay, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and in vitro chromosomal aberration assay in human lymphocytes), as well as summaries of pharmacodynamic interaction potential and pharmacokinetic interaction potential. The studies and information described for DURAGESIC is not relied upon for approval, as genetic toxicology studies were conducted for ACTIQ and the proposed label contains only this information. Therefore, listing DURAGESIC as a RLD and submitting patent certification is not considered necessary from the nonclinical standpoint.

Regulatory Summary (Nonclinical)

The IND was initially opened by Atrix Laboratories, Inc. in June 2001. Prior to submission of the IND, a pre-IND meeting was held with the Sponsor in May 2001 at which time the nonclinical program to support the initial IND as well as chronic clinical studies and submission of the NDA. It was agreed that a 30-day repeat-dose toxicology

study in a single species would be sufficient for support of phase 3 clinical studies and NDA submission. Advice included the directive that such studies should utilize the same dosing regimen to be used in humans and would ideally utilize the clinical product.

Additional requirements communicated to the Sponsor were the need for a pre- and postnatal developmental (Segment III) reproductive toxicity study due to the absence of this information in the literature and the potential for fentanyl neurotoxicity in the developing CNS, and carcinogenicity studies in 2 rodent species. This was countermanded at the Office Director level and a subsequent nonclinical agreement in January 2005 with Arius Pharmaceuticals, who replaced Atrix as the IND holder, was that reproductive and carcinogenicity studies would not be required by the Agency to support this 505(b)(2) application as long as "there was no change to the dosage form, total dose or duration of the intended treatment or patient population". A subsequent Type C meeting held with the (now current) Sponsor of the IND, BioDelivery Sciences International, contained several nonclinical statements and agreements:

1) the impurity [redacted] is not considered a structural alert for mutagenicity and therefore may be regulated according to ICH Q3A/B thresholds; b(4)
2) excipients are considered qualified by oral route;
3) the nonclinical study conducted in support of the NDA – the 28-day buccal toxicity study in the dog – is inadequate as it does not reflect the proposed clinical usage of the product; however, due to the severity of the indication, the clinical data which had been developed, the monitorability of local tolerance in clinical trials and with approved usage, repeat of the study will not be required though the Sponsor was told to utilize this as well as previous nonclinical studies conducted by legacy Sponsors in combination with information in the public domain to provide nonclinical support for the NDA.

Literature provided did not reference drug products and/or was not relied upon for approval.

II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW

Primary review of the application was carried out by Gary P. Bond, Ph.D. DABT. Major issues identified in review related to the manifestly substandard and non-supportive 28-day repeat-dose local tolerance study in dog which was performed by [redacted] b(4) on behalf of a previous Sponsor, Atrix Laboratories, Inc. Study deficiencies included: 1) clinical product was not used; 2) dose strengths studied did not cover the proposed clinical strengths (single strength 273 μg fentanyl buccal film used vs. the maximum proposed fentanyl strength of 1200 μg for ONSOLIS); 3) administration did not cover the proposed clinical frequency (BID vs. QID for ONSOLIS), 4) the product was rotated between sites on opposite sides of oral cavity (morning and evening) which does not mimic the use of the clinical product which may be applied to the same site regularly. Additional issues were the small group sizes (n=3/sex/group), and demonstration of significant CNS toxicity, the latter issue which may have been somewhat limiting as to dose but would have been avoided with a dose-titration/tolerance run-in portion to the study.

Although a repeat of the study using appropriate dose levels, formulation, dosing frequency, and animal numbers would be ideal in support of the application, sufficient clinical experience is considered to be available with the long systemic use of fentanyl as described in the public domain, data from ACTIQ, and development of a local tolerance safety profile from clinical trials of ONSOLIS as well as from information from transmucosal ACTIQ. Therefore, as reflected by prior agency agreement with the Applicant, a repeated local tolerance study is not a condition for approval.

III. RECOMMENDATIONS

A. Recommendation on approvability

I concur with the primary review of Dr. Gary Bond that the application may be approved.

B. Recommendation for nonclinical studies

No further nonclinical studies are recommended.

C. Recommendations on labeling

Final labeling remains to be negotiated with the Applicant. However, I am in general agreement with the labeling recommendations of Dr. Bond. As the plasma exposure of ONSOLIS is generally equivalent to ACTIQ at the respective maximum strengths (1200 µg vs. 1600 µg), the use of identical language from the approved nonclinical sections of the ACTIQ label with the exception of adjusted safety margins based on a mg/m^2 basis while technically correct is not acceptable. The use of larger safety margins for ONSOLIS as compared with ACTIQ, due to the former's greater bioavailability and hence lower maximum strength, is not scientifically supported. Safety margins should be identical to that of the ACTIQ label though for clarity the mg/m^2 unit should be eliminated and the safety margins can be expressed as *X-times the maximum recommended human dose (MRHD) of ONSOLIS.*

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/s/

Adam Wasserman
7/21/2008 02:56:18 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-266**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**10/31/07**
PRODUCT:	**ONSOLIS™ (fentanyl buccal soluble film)** **BEMA™ Fentanyl** [redacted] b(4) [redacted] - name during IND development
INTENDED CLINICAL POPULATION:	**management of breakthrough pain in cancer patients for their underlying persistent cancer pain who are already receiving and who are tolerant to opioid therapy**
SPONSOR:	**BioDelivery Sciences International**
DOCUMENTS REVIEWED:	**eCTD**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products**
PHARM/TOX REVIEWER:	**Gary P. Bond, Ph.D., DABT**
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PROJECT MANAGER:	**Kimberly Compton, R.Ph.**

Date of review submission to Division File System (DFS): **July 1, 2008**

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Background & Regulatory Issues

ONSOLIS™ is proposed for use in management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying, persistent cancer pain. Reference listed drugs (RLDs) in this 505(b)(2) application are DURAGESIC® (NDA 19-813 - a fentanyl transdermal system for use in management of pain in patients who are already receiving and who are tolerant to opioid therapy for their persistent, moderate to severe chronic **pain) and ACTIQ® (NDA 20-747 – a fentanyl** citrate oral transmucosal lozenge **for the same indication as ONSOLIS™).**

ONSOLIS' BioErodible MucoAdhesive (BEMA™) technology is a bilayer, bioerodible, mucoadhesive system of water-soluble polymers formulated into small discs containing fentanyl citrate as the active drug. The inner pink layer, into which the drug is loaded, is an erodible bioadhesive polymer matrix that remains in contact with the buccal mucosa after application while eroding and releasing drug into the mucosa. The outer white layer is a backing film that minimizes loss of drug into the oral cavity. The BEMA Fentanyl disc is designed to bioerode within approximately 30 minutes in humans, delivering fentanyl via the buccal mucosa so as to avoid hepatic presystemic metabolism. The rate of bioerosion is controlled primarily through the composition of the backing layer.

II. Recommendations

A. Recommendation on approvability

NDA approval is recommended.

B. Recommendation for nonclinical studies

No additional studies recommended for this medical indication and 505(b)(2) submission. All submitted nonclinical data is consistent with preNDA submission agreements for submission and approval of the NDA. Additional indications will require appropriate nonclinical studies consistent with these agreements and with ICH M3 Guidance for Industry: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals; ICH-M3 (Jul 1997).

C. Recommendations on labeling

The proposed label is based on the labels for NDA 20-747 (ACTIQ®) and NDA 19-813 (DURAGESIC®). The nonclinical-based labeling sections related to animal:human dose ratios should match those of NDA 20-747 (ACTIQ®).for sections 8.1 (Pregnancy) and 13.1 (Carcinogenesis, Mutagenesis, Impairment of

Fertility) because at the highest approved doses, the total bioavailability of **ACTIQ® and ONSOLIS™ result** in equivalent human exposure to fentanyl.

On this basis, for section 8.1 (Pregnancy), changes should be made as follows:

b(4)

See the entire Pham/Tox-based labeling sections 8.1 (Pregnancy) and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) at the end of the full review.

II. Summary of nonclinical findings – reference drugs Actiq® (NDA 20-747) and Duragesic® (NDA 19-813)

A. Brief overview of nonclinical findings

The nonclinical human safety assessment is based on comparison of the drug product to the reference drugs, for which clinical safety data is available to support the proposed dosing and indication.

A 28-day, repeat-dose toxicity study of fentanyl citrate and three local tolerance studies evaluating the test article administration site after a single dose (two with fentanyl citrate and one with fentanyl free base) were performed in dogs to evaluate the safety of BEMA Fentanyl disc formulations in support of clinical trials. Clinical observations noted in all test article-treated groups included decreased activity, excessive salivation, brown mucous in feces, abnormal gait and stance, emesis, and tremors. These findings were not unexpected and were related to the known pharmacological activity of fentanyl. There were no newly identified systemic or local adverse effects observed in these studies.

The pharmacokinetics of the ONSOLIS™ (aka BEMA Fentanyl ——— discs were evaluated in three Good Laboratory Practice (GLP) and 57 non-GLP formulation screening studies using the dog as a model. The studies, performed to determine the effects of formulation variables ——————— and stability on the pharmacokinetics (PK) of **BEMA Fentanyl discs, resulted in the current form of the submitted ONSOLIS™** drug product. PK data were not used in the nonclinical safety assessment as the local tolerance and repeat dose studies **with ONSOLIS™ did not test adequate** doses and frequency of administration to be able to determine comparative safety margins.

b(4)

b(4)