REVIEW
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Review: NDA 21-947/S005 Fentora (fentanyl buccal tablet, FBT), Supplemental New Drug Application (sNDA)

Indication: Management of breakthrough pain in patients who are regularly taking around-the-clock opioid medicine for their underlying persistent pain

Company: Cephalon, Inc

Submission: NDA 22-224 is located in the EDR. The submission includes a section titled 'Abuse Liability Assessment' (found under Module 5.3.5.4)

This review provides recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) regarding the abuse and diversion potential of Fentora.

Summary:

Cephalon, Inc. has filed this 505(b)(2) supplemental New Drug Application (sNDA 2 1-947) in support of registration of Fentora (fentanyl buccal tablet, FBT) C-II for the treatment of break-through-pain (BTP) in opioid tolerant non-cancer patients with chronic pain. Fentora is one of the most potent and rapidly absorbed μ opioid agonists currently approved for use in an unsupervised patient setting.

Background:

Fentora was initially approved on September 25, 2006, for the treatment of breakthrough pain in opioid tolerant patients with cancer with a proposed Risk Minimization Action Plan (RiskMAP) to minimize three identified risks: 1) use of the product by non-tolerant individuals; 2) misuse, abuse and diversion; and 3) unintended exposure.

sNDA 21-947 proposes five tablet strengths (100, 200, 400, 600 and 800 μg) for buccal mucosal administration and all are indicated for the management of breakthrough pain in patients with noncancer pain who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.

Fentanyl is estimated to be one hundred times as potent as morphine as an analgesic (Gutstein and Akil in Goodman & Gilman, 11th Ed., 2006). Fentanyl is controlled in Schedule II of the Controlled Substances Act (CSA) as are similar opiates approved for medical use, including hydromorphone, morphine, and oxycodone. Schedule II drugs have the highest potential of abuse and pose a high risk to the public health (21 U.S.C. 812)

Review:

The Controlled Substance Staff (CSS) in CDER has expressed concern about the safety risks for addiction, abuse and diversion, as evidenced by data acquired during clinical development of FBT, and has asked the sponsor for additional information by which to evaluate these risks. This CSS review is preliminary, as assessment of data and other information submitted by the sponsor under NDA 21-947 is ongoing. This review is limited to issues concerning the potential abuse and diversion of FBT; as the general review of safety for an expanded indication in the proposed patient population is covered by DAARP.

Information included in this review includes general summary data provided by the sponsor, quarterly safety reports and the report submitted with the expanded indication entitled "Review and Assessment of Risks for Abuse and Diversion"(Report Approval Date: 2 November 2007).

FBT Phase 3 studies

Table 1 summarizes the Phase 3 studies for the new supplemental indication. Only two of the studies were conducted for periods consistent with long term administration in chronic noncancer pain: 3052, a 12 week double-blind, placebo-controlled study and the open label, uncontrolled study 3040. The sponsor uses the total number of patients evaluable for safety (i.e., 941) as the denominator in its report on review and assessment of risks of abuse and diversion.

Table 1: FBT Phase 3 Studies in Opioid-Tolerant Patients with Chronic Noncancer Pain and Breakthrough Pain

Study type & number	Population	Study duration	Number of patients
Double-blind, placebo-controlled studies:			
Study 3052	chronic noncancer pain	12 week	104
Study 3041	chronic neuropathic pain	< 4 weeks	79
Study 3042	chronic low back pain	< 4 weeks	77
Open-label, uncontrolled study:			
Study 3040	chronic noncancer pain	Up to 18 months	727
Total number of patients evaluable for safety			**941**

All patients entered the FBT studies while taking an around-the-clock (ATC) opioid and were managing BTP using an opioid. All patients were screened and required to meet protocol-specified entry criteria. In an attempt to screen out patients who might be at higher risk of abuse or addiction, those with a recent history (within 5 years) or current evidence of alcohol or substance abuse were excluded. In addition, all patients underwent a urine drug screen (UDS) and were excluded if there was evidence of an illicit substance or a medication for which there was no legitimate medical explanation. Patients could be excluded if in the opinion of the investigator, the patient had a psychiatric condition that would compromise their safety if they participated in the study. While there were no scheduled UDS during the study after the screening visit, investigators were permitted to conduct a UDS at anytime at their discretion.

Abuse Potential

The sponsor's report entitled "Review and Assessment of Risks for Abuse and Diversion" (Report Approval Date: 2 November 2007) reviews the events of abuse, addiction, and overdose that have been reported in FBT clinical studies of opioid-tolerant patients with chronic noncancer pain and BTP. A number of publications in the literature have identified aberrant drug-use

behaviors within patients with noncancer-related pain who were taking opioids (Table 2 lists these behaviors, as identified in the sponsor's review of the literature). The sponsor reviewed their clinical database retrospectively for evidence of these behaviors that may be precursors or signs for abuse. They considered the following behaviors as 'high risk': abuse/dependence, overdose and urine drug screen (UDS) that was positive for an illicit substance or a medication for which there was no legitimate medical explanation. The results of this evaluation are summarized in Table 3.

Table 2: Types of Aberrant Drug-use Behaviors (as identified by the sponsor)

Abuse/Dependence	Study drug theft
Overdose	Lost to follow-up
Motor vehicle accident	Seeking prescriptions from other sources
Fear of addiction	Lost study drug
Discharged from practice	Overuse of study drug
Positive UDS	Unapproved use of a medication used for another symptom
Unreliability	Acquiring opioids from other medical sources
Using nonprescribed medication	

Table 3: Summary of Patients by Risk Category

Risk Category	Number of Patients[¥]	Percent
High risk behaviors*	30	3%
Abuse/dependence	8	<1%
Overdose	9[#]	1%
Positive UDS	13	1%
Other Aberrant behaviors	126	13%
None	785	83%

[¥] Patients could have more than one aberrant behavior reported
*3 patients also had non-high risk aberrant behaviors
[#] includes one patient with 2 episodes of overdose

Overall, of the 941 patients in the safety analysis set, the sponsor reported that 3% of the FBT Phase 3 population exhibited 'high risk' behavior, and 17% (n=156) had at least one aberrant drug-use behavior. The majority of patients (132/156 or 85%) of these patients had only 1 behavior identified. The aberrant behaviors identified in more than 1% of patients in the safety analysis set were overuse of study drug (44 patients, 5%), study drug theft (35 patients, 4%), and lost to follow-up (33 patients, 4%) (Table 4).

Table 4: Aberrant Behaviors Identified in > 1% of Patients

Behavior	Number of Patients	Percent
Overuse of study drug	44	5%
Study Drug thefts	35	4%
Lost to follow-up	33	4%

In their conclusions, the sponsor indicated that the 17% incidence of adverse drug-use behaviors is lower than that reported in the observational studies in this population (Webster and Webster 2005; Chabal et al. 1997). They postulated that the difference was likely due to the differences between clinical studies and clinical practice. The sponsor's evaluation of possible baseline predictors of these behaviors revealed that younger patients and patients with a history of mania or psychosis were at higher risk of displaying one or more of the identified aberrant behaviors. Patients with a history of anxiety or mood disorders (prevalent conditions in this chronic pain population) did not appear to be at higher risk of having aberrant behaviors. Finally, the sponsor stated that the risk of developing an aberrant behavior was not affected by duration of treatment in the study.

Drug Diversion

During these clinical studies, thefts of drug from both individual patients and from the study centers were reported by the sponsor (Table 5). The sponsor noted thefts of study drug from 35 patients in studies 3040 and 3052, with no drug thefts occurring in the shorter duration studies (3041 and 3042). Police reports were made for 22 of the occurrences.

Table 5: Study drug thefts during the Phase 3 clinical trials

Study drug theft	Number of cases	Percent	Amount of drug stolen
From patient	35	4.2%*	----
From study center	5	---+	4,290,600µg¥

*Number of cases (5) divided by the total 831 patients (831) in studies 3040 and 3052.
+There were 69 study centers in study 3040
¥ Calculated from additional information provided by the sponsor on 03/21/08, expressed in total µg - see below

Study site	Number of tablets	Strength µg/tablet	Total Amount of Drug (µg)
011	24	600	14400*
031	306	800	244800
036	1038	100	103800
	834	200	166800
	1038	400	415200
	1038	600	622800
	834	800	667200
031	24	100	2400
	24	200	4800
	432	400	172800
	942	600	565200
	1350	800	1080000
018	88	400	35200
	124	600	74400
	151	800	120800

*This study site also reported that '4 x 6' was stolen in addition to the 24 x 600µg tablets, but did not provide further information (.e.g., whether these are individual tablets or packs of tablets). Thus, the provided calculation might represent an underestimation of the amount of drug stolen.

The sponsor indicated that patients were withdrawn when the risk of diversion or repeat theft was thought to be high, although the criteria for high risk were not provided. Five patients were withdrawn from the study, four from study 3040, and one from study 3052. Most of the thefts (30 of 35) were reported to have been perpetrated by people who did not have regular access to study drug, and 20 of the thefts were reported to have occurred outside the patient's home. The husband of one patient, who reportedly took the patient's study drug, was found dead of a possible FBT overdose.

Despite significant protocol precautions designed to ensure the safe delivery, handling and storage of study drug in accordance with local and federal regulations, 5 study centers participating in study 3040 reported thefts of study drug, which were reported to local authorities and to the DEA. Study drug was taken from locked cabinets in 3 of the thefts, including one where there were signs of forced entry. The study drug was lost in transit from the health facility distribution center to the pharmacy in one theft, and in the remaining case, unused study drug returned by a patient was subsequently missing during a drug accountability/return review.

Comments on the Sponsor's Analysis of Abuse and Diversion Potential Data

Our preliminary review of the sponsor's data indicated additional cases of potential abuse than the 30 identified as "high risk" by the sponsor in their report "Review and Assessment of Risks for Abuse and Diversion". Thus, the sponsor's interpretation and conclusions concerning potential health risks of fentanyl buccal tablet when used in non-cancer break-through-pain (BTP) are not consistent with the CSS assessment and underestimate this risk. As such, on March 12, 2008, we requested that the sponsor provide the following:

- Complete information as to how data associated with "aberrant drug behavior" were gathered and evaluated, including the specific categories assigned to particular subjects in the data set.
- Criteria for determining a 'high risk' behavior
- Confirmation of the denominator data (number of noncancer patients exposed to Fentora in trials).
- Specific details on the instances of study drug stolen from the 5 participating study centers in study 3040, including reports filed with DEA.
- Case report forms and all available information on the cases listed in the attached Table.

On March 21, 2008, we received the sponsor's electronic response to this request. We note that our evaluations of this recent information are still ongoing, but we have the following comments.

In our most recent request to the sponsor, we asked for additional information, including information on specific cases that we had found among those coded as noncompliance or protocol violations. These cases were not part of those evaluated in the aberrant drug-use behavior report, and included those categorized as overuse of study medication and did not return study medication and/or packaging.

The sponsor responded that they limited their aberrant behaviors to those identified in clinical practice, as they found no information specific to the clinical trial setting. Accordingly, they did not consider protocol requirements to return unused study medication or packaging as indicative

of an aberrant behavior. Likewise, there were other protocol specific instructions of which noncompliance was not considered indicative of abuse or addiction. Consequently "reports of noncompliance were not automatically considered aberrant drug behaviors unless there was sufficient information to indicate an aberrant behavior that would be observed in a clinical practice setting." In addition, the sponsor provided new information on several other cases of aberrant behavior, not included in their original report.

CSS has contacted the DEA to confirm information on the thefts from the study sites reported by the sponsor. DEA had information regarding these cases, and provided information on other thefts of Fentora that have occurred from pharmacies, including an armed robbery. CSS is awaiting detailed information and confirmation of these additional cases.

Conclusions:

While we agree that most instances of noncompliance do not automatically indicate aberrant drug-use behavior or substance abuse, instances where a study drug is not returned as required does indicate a problem with drug accountability, which could potentially signify abuse or diversion. This is especially important for a Schedule II drug wherein accountability is a requirement of DEA registrants. Although we requested additional information on how the data was gathered, this information has not yet been provided.

We are particularly concerned about the training provided to the clinicians running these trials as to their recognition of behavior deemed "aberrant" and the policies and procedures for capturing and coding such behavior, including the definitions of addiction, abuse, and diversion employed in these studies. These types of information are essential to providing accurate information for assessing potential abuse and addiction occurring in these trials. Because this information is not available or perhaps was not gathered, the rates of abuse, diversion, and aberrant behaviors, in general, are likely underreported for these clinical trials. Furthermore, because most individuals who would be at high risk for substance abuse were excluded from participation in the Phase 3 clinical trials, the rates of these behaviors are not representative of what could occur if FBT were approved for expanded use in the general population with chronic pain.

Based on the information available to date, CSS finds that:

- The risks of unintentional potentially fatal overdose, as well as of misuse or abuse of fentanyl, and of FBT in particular, are extremely high, even when compared to risks posed by other transmucosal fentanyl products.
- Events observed in clinical trials illustrate the significant risks of overdose, misuse, abuse, and diversion from FBT. Detection of aberrant drug use behavior in the controlled setting of a clinical trial is very unusual and raises concern for the safe use of this drug in the general outpatient setting. It is particularly noteworthy in that "high risk patients" - those with a prior history of drug or alcohol abuse or those with a positive drug test - were excluded from participation in the clinical trials.
- It is of particular concern that aberrant drug use behavior in the sponsor's clinical trials appears to be much more frequent in the noncancer population who used Fentora long term.

- Finally, the signals obtained in postmarketing surveillance where the off label uses differed from the currently approved Fentora indication (treatment of breakthrough pain in opioid tolerant patients with cancer) resulted in serious adverse events, including deaths.

Taken together, these findings suggest that expanded use of this product will raise serious safety concerns, and additionally result in significant abuse and diversion that further impacts the public health and safety.

Abbreviations and Acronyms:

around-the-clock	ATC
break-through-pain	BTP
Controlled Substance Staff	CSS
Controlled Substances Act	CSA
Division of Anesthesia, Analgesia and Rheumatology Products	DAARP
fentanyl buccal tablet	FBT
Supplemental New Drug Application	sNDA

Date: April 1, 2008

Primary Reviewer: Lori Love, M.D., Ph.D., Medical Officer
Controlled Substance Staff (HFD-009)

Secondary Reviewer: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Concurrence by: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)