

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-947

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: September 25, 2006

DRUG: FENTORA (Fentanyl Citrate Buccal Tablets, equivalent to fentanyl free base 100, 200, 400, 600 and 800 mcg)

NDA: 21-947

SPONSOR: Cephalon Inc.

INDICATION: For the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain

Cephalon Inc. submitted NDA 21-947 on August 31, 2005, in support of marketing approval for FENTORA, for the treatment of breakthrough pain in opioid-tolerant cancer patients on around-the-clock opioid background treatment. An approvable letter was issued on June 29, 2006. For a summary of the Agency's findings and determination based on our review of the original application, see my memo dated, June 29, 2006. The only aspect of the application that formed the basis for the approvable action, (rather than an approval action), was the fact that the sponsor's RiskMAP had not been submitted in a form that could be considered complete and final for Agency review. On July 25, 2006, the sponsor submitted their response to the approvable letter. This submission consisted of a RiskMAP that contained all of the components that would constitute a complete and final plan and therefore was considered a complete response.

The FENTORA RiskMAP has been thoroughly and meticulously reviewed by the Division review team, the Office of Surveillance and Epidemiology review team, the Controlled Substances Staff review team, and the Division of Drug Marketing, Advertising and Communications review team. Numerous shortcomings in the proposed plan were noted by each of the teams and the Agency's concerns were forwarded to the sponsor. After a series of discussions and resubmissions, a final RiskMAP has been

submitted and is now considered to be acceptable to the Agency. Documentation of these interactions and the approval of the final product by each of the above noted teams has been filed in the CDER Document Filing System, including a thorough compilation and review of the final sign-offs by the different review teams in a memo filed by the FENTORA application Project Manager, Kim Compton, on September 28, 2006.

The FENTORA RiskMAP is comprised of carefully crafted programs designed to address the potential for misuse, accidental exposure (particularly by children), abuse and diversion of the product. As I stated in my June 29th memo, there are significant dangers and safety concerns that are inherent with any potent opioid drug product. However, these dangers and concerns must be weighed against the value of the product for the intended patient population. As breakthrough cancer pain is a devastating condition that is often unresponsive to the available approved analgesic products, and as FENTORA appears to be safe and effective when administered properly in this population, the Agency has made every effort to maximize the benefit-risk considerations for FENTORA by limiting the risks associated with its improper use via the negotiation of a thorough RiskMAP with the sponsor. During the extensive discussions, Agency experts in the treatment of pain, the management of controlled substances, and in epidemiology, surveillance and risk communication worked with the sponsor to develop a final plan that is state of the art in its scope and mechanisms to maximize risk prevention for this type of product. The plan also incorporates numerous features designed to assess its success or failure in the post-marketing period, including the submission to the Agency of periodic reviews of extensive data that will be collected by surveillance, and from longitudinal databases, safety reports and other sources. Additionally, the FENTORA RiskMAP incorporates plans for appropriate intervention should signals of misuse, accidental exposure, abuse or diversion become apparent in the post-approval period.

FENTORA provides a useful and, therefore, important addition to the analgesic armamentarium for patients suffering unbearable pain due to cancer. While no efforts at the risk management of opioid analgesic drug products, such as FENTORA, are likely to be one hundred percent effective, the extensive and thorough RiskMAP for FENTORA will clearly minimize the number of accidental exposures, as well as the misuse and abuse of the product. Since no plan will be fully successful, it is important to note that, should a concerning signal develop in the post-marketing period, the plan will allow the sponsor and the Agency to act quickly to intervene. Given this RiskMAP and the importance of the addition of FENTORA to the cancer pain armamentarium, I recommend that this drug be approved for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
9/25/2006 05:24:27 PM
MEDICAL OFFICER



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Medical Officer's Review of Complete Response to Approvable Letter

NDA #:	21-947
Drug Name (generic):	FENTORA (fentanyl buccal tablets)
Sponsor:	Cephalon
Indication:	Management of breakthrough pain in opioid-tolerant cancer patients
Type of Submission:	Complete response to approvable letter
Dates of Submission:	25 July 2006 and 11 September 2006
Review Date:	15 September 2006
Material Reviewed:	Submissions dated 7/25/06 & 9/11/06, consults from OSE and CSS
Reviewer:	Robert B. Shibuya, M.D.
Project Manager:	Kimberly Compton, R.Ph.

Background

FENTORA is a reformulation of oral transmucosal fentanyl citrate (OTFC). The applicant, Cephalon, is seeking an indication of the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying cancer pain.

The initial NDA (21-947) was submitted on 31 August 2005. The Division took an Approvable action on this application on 29 June 2006. There were no questions of efficacy or safety and the labeling (package insert and Medication Guide) had been negotiated successfully with the input and concurrence of pertinent internal parties [the Office of Surveillance and Epidemiology (OSE), Controlled Substance Staff (CSS), and Division of Drug Marketing, Advertising, and Communication (DDMAC)].

The one issue that precluded the approval of NDA 21-947 was that Cephalon was not able to submit a finalized, complete Risk Minimization Action Plan (RiskMAP) before the PDUFA date. The Division took an Approvable action with the understanding that the applicant would finalize the RiskMAP in a timely fashion and submit it. The Division agreed that the resubmission would be considered a Class I resubmission with a 2-month deadline.

Event	Date	Comments/Agreements
		<p>4. <i>Cephalon must not "undo" important safety messages contained in the MedGuide.</i></p> <p>5. <i>Language that might imply: _____ is unacceptable.</i></p> <p>6. <i>Information on the website must be consistent with the approved labeling.</i></p> <p><i>Cephalon provided some clarification regarding how it will use sales data.</i></p>
CSS consult finalized	9/1/06	See Dr. Hertz' memo to file for details.
<u>Discipline letter sent to Cephalon</u>	9/7/06	<u>Comments from CSS regarding the revised RiskMAP were sent verbatim. Again, see Dr. Hertz' memo for details.</u>
<u>Division RiskMAP comment letter sent to Cephalon</u>	9/7/06	<p><u>Cephalon should:</u></p> <ol style="list-style-type: none"> 1. <u>Remove any element with potential promotional qualities from the RiskMAP.</u> 2. <u>Remove any presentation of information that implies _____</u> 3. <u>Ensure that the patient population is limited to "opioid-tolerant cancer patients."</u>
Email from Cephalon addressing CSS discipline letter	9/10/06	Cephalon addressed CSS' comments point by point, providing a more detailed response or remedy where appropriate. These changes were reflected in the September 11, 2006 resubmission of the revised RiskMAP (below).
Cephalon submits written response to all comments to date (revised RiskMAP)	9/11/06	<p>Cephalon has complied with all recommendations from the discipline letters. Most importantly, Cephalon has</p> <ul style="list-style-type: none"> • Included a commitment to report adverse events of interest (accidental exposures, deaths, medication errors, etc) as 15-day safety reports. • Specified that the product is only for use in opioid-tolerant <u>cancer patients.</u> • Removed (almost all, see below) references to _____ • Added a section regarding thresholds _____ • Revised _____

Event	Date	Comments/Agreements
		<p style="text-align: center;">/ / /</p>
<p><i>Telecon with Cephalon (preceded by internal meeting)</i></p>	<p>9/13/06</p>	<p><i>CSS comments for Cephalon:</i></p> <ol style="list-style-type: none"> 1. <i>With regard to the definitions for intervention section (page 42 of the RiskMAP, 9/11/06), use "unique recipients (URDD)" as the denominator in the incidence calculation (OSE concurred).</i> 2. <i>In the DOSAGE AND ADMINISTRATION section, CSS had recommended adding a sentence reading "Patients should use up all tablets before increasing to a higher tablet strength." Since this instruction conflicted with other instructions for use, CSS recommended that this sentence be replaced with language to the effect that patients should dispose of unused/extra product as quickly as possible (exact wording to be negotiated) at the next printing of the package insert (PI).</i> <p><i>OSE comments for Cephalon:</i></p> <ol style="list-style-type: none"> 3. <i>With regard to the thresholds, _____ (page 42 of the RiskMAP), Cephalon originally proposed to investigate if a signal (misuse, abuse, diversion, deaths, accidental exposures) was observed over 3 consecutive quarters. OSE wanted this shortened to 2 consecutive quarters. FDA and Cephalon agreed that Cephalon will submit data quarterly. During the first year of marketing, no specific criteria were set for a mandatory intervention although FDA reserves the right to require Cephalon to investigate regardless of the number of quarters of trending. Following the first year of marketing, increased signals over _____, would prompt an _____.</i> 4. <i>ALL medication errors must be reported as 15-day expedited safety reports. All unintentional (where the child is not the patient) pediatric exposures must be reported as 15-day reports. Exposures of children under age 16, where the product was intentionally prescribed, will be noted as off-label use.</i> 5. <i>A few examples of _____ were noted (see DDMAC consult for details). It was agreed that _____ would be removed in the future and in the RiskMAP.</i>

Event	Date	Comments/Agreements
		<p>6. The website should provide more detailed information regarding how to use the product. The Q & A About Fentora for Patients (Tool 15) has a drawing of a</p> <p style="text-align: center;">/ / /</p> <p>DDMAC comments for Cephalon. DDMAC had several comments, some of which overlapped with OSE. Among other comments, DDMAC requested:</p> <p>7. Add the definition of "opioid-tolerant" to appropriate sections of the RiskMAP.</p> <p>8. Ensure that it is clear that _____</p> <p>9. Ensure that the full Boxed Warning is appropriately represented.</p> <p>CONCLUSIONS</p> <ul style="list-style-type: none"> • Cephalon agreed with all comments as described above. • Cephalon was told that the proposed edits to the _____ and the minor edit in the Clinical Pharmacology section (striking of comma) were acceptable. • Cephalon was instructed to submit the RiskMAP documents that require revision ASAP. • Cephalon was advised to expect further comments from CSS. • With regard to changes that were made to the package insert and medication guide, FDA agreed that the changes could be made upon the next printing of those documents. HOWEVER, Cephalon was told that it must commit <u>in writing</u> to submit a labeling supplement proposing the agreed-upon changes to the package insert and medication guide, immediately upon approval of FENTORA.
Cephalon submits RiskMAP elements revised per the telecon of 9/13/06	9/14/06	This email included a list of the negotiated agreements made during the 9/13/06 teleconference. In addition, essentially all of the tools that required editing were attached (no _____ were attached).

*Division of Medication Errors and Technical Support (OSE)

Reviewer Comments

In these submissions and in teleconferences, Cephalon has adequately addressed the deficiency noted in the Approvable Letter. Furthermore, in addition to other changes to the RiskMAP, the Division has negotiated the following important agreements:

1. Cephalon will not use the terms _____
2. Cephalon will not make _____
3. Cephalon will not use language that might cause patients to use the product improperly (i.e. _____)
4. Cephalon will not use language that might imply _____
5. Cephalon will not _____

At the time of the writing of this review, this reviewer notes that the applicant must still submit the amended labeling (Package Insert and Medication Guide) that will go into effect with the next printing.

Assuming that, prior to approval, Cephalon provides acceptable versions of the labeling to be changed with the commitment to submit the amended labeling upon approval this reviewer recommends that FENTORA be approved with the labeling attached to the June 2006 Approvable Letter.

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/s/

Robert Shibuya
9/15/2006 12:50:30 PM
MEDICAL OFFICER

Sharon Hertz
9/15/2006 05:57:45 PM
MEDICAL OFFICER
I concur.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS

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MEMO TO FILE

DATE: September 5, 2006

TO: NDA 21-947

THROUGH: Bob Rappaport, M.D., Division Director DAARP, CDER

FROM: Sharon Hertz, M.D., Deputy Director, DAARP, CDER (HFD-170)

RE: Consultation from the Controlled Substances Staff Addressing the Complete Response to Approvable Action Dated July 25, 2006

Background

On June 29, 2006, the Division took an Approvable action on FENTORA (NDA 21-947, fentanyl buccal tablets). The package insert and medication guide had been reviewed by the review division, the Controlled Substances Staff (CSS) and the Office of Surveillance and Epidemiology (OSE) and requested changes by the Agency were negotiated with the applicant and agreed upon during this review cycle. The only deficiency precluding an Approval action was that the applicant was unable to finalize all of the elements of the Risk Minimization Action Plan (RiskMAP) prior to the PDUFA date.

On July 25, 2006, the applicant submitted a Complete Response to the Approvable Letter consisting of what the applicant believes to be a complete, final RiskMAP without any changes to the package insert or medication guide.

A consultative opinion was requested from CSS and OSE regarding the current submission. The CSS consult was finalized on September 1, 2006. A discipline review letter with the CSS comments inserted verbatim was conveyed to the sponsor on September 7 2006.

There are several areas where CSS requests changes to the package insert and medication guide. As these have not changed since the Approvable Action on June 29, 2006, the only basis for recommending changes now would be the discovery of new safety concerns. Each comment in the CSS is addressed with a reviewer comment.

CSS comment:

1) Effervescent Technology

Under the "Description" section, 3rd paragraph, first sentence, delete the end of the sentence that

This sentence, which currently reads: "utilizing an effervescent reaction which is thought to enhance the rate and extent of fentanyl absorbed through the buccal mucosa," does not contribute to the safe and effective use of Fentora.

In the June 23, 2006 telecom, the Sponsor agreed not to use the term "effervescent" in describing the formulation. The Sponsor also agreed not to make reference to the

Proposed language such as "enhance the rate and extent of fentanyl absorbed through the buccal mucosa" in the label may increase the appeal for abuse by certain individuals who abuse or use opioids recreationally. CNS active drugs with rapid onsets of action are associated with greater subjective effects that relate to increased likelihood of drug abuse.

Promotional claims related to _____, should be removed. Considering the risk of fatal overdose associated with the misuse and abuse of Fentora, any claims that refer to _____ should not be allowed. These claims defeat the purpose and goals of the RiskMAP.

Reviewer comment:

I concur that any and all promotional claims _____ are unsubstantiated by data from adequate and well controlled trials. This comment has been conveyed to the applicant in writing (letter dated August 30, 2006) and during a teleconference on August 31, 2006. However, the language in the Description section describing that an effervescent reaction may be responsible for enhancing the pharmacokinetic parameters was discussed in a meeting with the Chemistry, Clinical Pharmacology, DDMAC, OSE, and CSS teams present and was determined to be accurate as written.

CSS comment:

2) Quantities of tablets dispensed during titration and maintenance

a) Titration

CSS recommends inclusion of the following paragraph under "Administration of Fentora" section, as proposed by the Sponsor in their June 16, 2006 submission. The purpose of the paragraph was to maximize patient convenience, enhance patient safety, and minimize the risk of abuse and diversion:

"Patients should be prescribed an initial supply of no more than 28 (100mcg) tablets, thus limiting the number of tablets in the home during titration. Patients should use up all tablets before increasing to a higher dose."

b) Maintenance

CSS recommends including a statement related to the quantity of Fentora that will be dispensed and available in the patient's home during both titration and maintenance. The Sponsor needs to add a sentence to recommend the dispensing of no more than one month supply of Fentora.

CSS is concerned about the risks associated with abuse and misuse stemming from the availability of large amounts of Fentora in the patient's house.

CSS is also concerned about the _____, presented by the Sponsor in proposed marketing brochures. The brochures indicate _____

Once again, this type of promotional activity defeats the goals of the RiskMAP.

Reviewer comment:

I concur that the _____ included in the marketing brochures that were also included in elements of the RMP are inaccurate and inappropriate. The dosing instructions for the safe use of Fentora do not consist of _____. Rather, the proper dosing instructions must describe the use of one tablet for an episode of breakthrough pain, that it must not be repeated before a minimum of 30 minutes have elapsed, and that additional instructions individuated for each patient are likely appropriate as well. This was discussed during the teleconference on August 31, 2006 and conveyed to the applicant in a Discipline review letter with comments for OSE dated August 29, 2006.

There is no basis for an *a priori* limit to the number of tablets to be dispensed to a patient. Cancer patients with breakthrough pain may require three, four or more tablets daily depending on the extent of disease and ability to control pain with around-the-clock opioids. Progression of disease may result in worsening of pain. It is up to the clinician caring for the patient to determine the amount of breakthrough pain medication that is appropriate to prescribe. The currently package insert emphasizes that there is a risk for abuse and misuse associated with the use of Fentora. The package insert currently includes the following language which provides adequately informs the prescriber and specifically provides language to inform patients of this risk:

Boxed Warning

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. **FENTORA** can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing **FENTORA** in situations where the

physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

***FENTORA* is intended to be used only in the care of opioid tolerant cancer patients and only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.**

Information for Patients

-Patients and caregivers should be advised that if they have been receiving treatment with *FENTORA* and the medicine is no longer needed they should contact Cephalon at 1-800-896-5855 or flush any remaining product down the toilet.

Patients should be warned that the active ingredient in *FENTORA* is fentanyl which is a drug that some people abuse. *FENTORA* should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.

Dosage and Administration

To reduce the risk of overdose during titration, patients should have only one strength *FENTORA* tablet available at any one time. Patients should be strongly encouraged to use all of their *FENTORA* tablets of one strength prior to being prescribed the next strength. If this is not practical, unused *FENTORA* should be disposed of safely (see Disposal of *FENTORA*).

Safety and Handling

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed. Instructions are included in **Information for Patients and Their Caregivers** and in the Medication Guide. If additional assistance is required, referral to the *FENTORA* 800# (1-800-896-5855) should be made.

Additionally, the medication guide warns patients that, “Fentora is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.” and, “Prevent theft and misuse. Keep Fentora in a safe place to protect it from being stolen since it can be a target for people who abuse narcotic medicines or street drugs.”

CSS comment:

3) Editorial change to clarify the potential misunderstanding that Fentora had been administered intravenously.

Under the "Clinical Pharmacology" section, "Respiratory System" subsection, 2nd paragraph, modify 2nd sentence that reads, "Although not observed with oral transmucosal fentanyl products, in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration."

Reviewer comment:

This language is standard for fentanyl package inserts and describes an unusual phenomenon that can occur upon intravenous administration of fentanyl. It is present to indicate this phenomenon has not been observed when fentanyl is administered by the transmucosal route.

CSS comment:

4) Type of information offered through the toll free number listed in the label Provide information regarding the type of advice that will be provided through the toll free number listed under "Information for Patients and Their Caregivers", item number 10 I (sic)

Reviewer comment:

I concur that this information should be elucidated. This has been conveyed to the sponsor

CSS comment:

Medication Guide

CSS recommends strengthening warnings against sharing Fentora and the risk of respiratory depression and death associated with misuse and abuse

1) Under the "What is FENTORA" section, the warning that "FENTORA should not be given to anyone else, even if they have the same symptoms, because this medication may harm or even kill the person for whom it has not been prescribed", should be more prominent and deserves a separate paragraph.

2) The medication guide should clearly state the risk of respiratory depression and death associated with the misuse (taking not as prescribed) and abuse of this product.

3) Respiratory depression should be explained clearly in lay language.

4) Under the "How should I store Fentora?" section, modify first bulleted

paragraph to indicate that Fentora should always be stored in a secure place, away from children and from anyone for whom it has not been prescribed.

5) All educational materials provided by the Sponsor should include warnings not to share Fentora or use it to treat other types of pain, such as pain not associated with cancer.

Reviewer comment:

The medication guide has been fully vetted during the first review cycle by all disciplines, including the Division of Medication Errors and Technical Support of OSE. The information requested by CSS is all present in the medication guide as it is currently written. Furthermore, all patient information must include the language of the medication guide without any risk minimization.

CSS comment

RiskMAP

CSS requests from the Sponsor the following:

- 1) Submit proposed format and content (draft outline of the tables and data elements) of the quarterly report for FDA review. The proposed RiskMAP does not clearly indicate what kind of events will be included in the quarterly submissions.
- 2) Commitment from the Sponsor to submit expedited reports for the following:
 - All reports of death as the outcome,
 - All pediatric (0-16 years of age) exposure reports, regardless of intention and outcome,
 - All serious adverse events associated with medication errors, misuse, abuse and addiction.
- 3) Describe the procedures that will be used to assess off label use of the product. Include assessment of off-label use in quarterly reports as done with Actiq.
- 4) Clearly propose interventions and specify quantitative thresholds for signals that will prompt those interventions and revisions to the RiskMAP during the post-marketing surveillance period.
- 5) Clarification of the role and responsibilities of the Cephalon External Advisory Board as well as its interaction with the FDA.
- 6) Quarterly reporting is acceptable for the first two years. Frequency of the reporting after the first two years will be determined in consultation with the FDA based upon post-marketing experience.
- 7) Cephalon proposes to use DAWN Live! as a source of medical examiners' data. This proposal is unacceptable because DAWN Live! **does not** provide access to

medical examiner/coroner data (SAMHSA limits access to the ME data to the medical examiners who submit the data).

8) Cephalon proposes to use DAWN Live! to monitor emergency department admissions for their product in comparison to other opioid products, and to analyze patterns regarding geographic locations, age groups, drug combinations and other risk factors. This proposal is methodologically flawed in that DAWN Live! data generally cannot be used to measure trends because participation of hospitals, and the completeness of their data, vary. The unweighted DAWN data are not representative. In addition pharmaceutical companies can use DAWN Live! only to look at their own products at the brand level. Sponsors cannot make comparisons with other companies' brands and don't get access to any geographic location information. DAWN Live! does not have the capacity to provide information about drug combinations (polydrug ED visits).

9) The Sponsor should use DAWN Live! data as a warning system to track ED visits associated with the use of Fentora in comparison to Actiq which is also their product.

10) Sponsor should provide information on how it is planning to capture fatalities associated with the use of their product.

11) Educational materials for both the physician and patient should be revised and the Sponsor should honor commitments made at the June 23, 2006 telecom.

12) Overall, the educational pieces should incorporate a stronger message to convey the risks of overdose associated with the product.

III- Proposed Website

1) More emphasis on risks of overdosing or sharing this medication.

2) Remove _____

3) It has been noted that the Fentora health care providers' web site _____

Reviewer comment:

These items have all been conveyed to the applicant either in the discipline review letter of August 29, 2006, the division letter of August 30, 2006, the teleconference of August 31, 2006 and/or the discipline review letter of September 7, 2006.

Conclusions:

As noted above, many of the concerns raised in the CSS consult for the complete response submitted to NDA 21-947 are shared by the division and the OSE. These concerns have been conveyed to the applicant. The requested labeling changes to the package insert and medication guide by CSS have been thoroughly reviewed and considered in the context of the current language present, and the basis for the proposed changes. Many of the requests for greater emphasis cite language that is already very prominent in the package insert and the medication guide. There do not appear to be data-based safety concerns from the clinical trials to support the changes to the Dosage and Administration section, and in particular, the requested limits to dispensing product may clash with effective management of patients with severe cancer breakthrough pain.

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Sharon Hertz
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: June 29, 2006

DRUG: FENTORA (fentanyl buccal tablets), as the citrate and equivalent to fentanyl free base 100, 200, 400, 600 and 800 mcg

NDA: 21-947

SPONSOR: Cephalon Inc.

INDICATION: For the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain

Cephalon Inc. has submitted NDA 21-947 in support of marketing approval for FENTORA, for the treatment of breakthrough pain in opioid-tolerant cancer patients on around-the-clock opioid background treatment. This product is a new formulation of Actiq, oral transmucosal fentanyl citrate (OTFC), approved in 1998 for the same indication, which consists of a lozenge on a stick that is rolled along the oral mucosa where it is absorbed, until such time as relief of pain or intolerable side effects occur; residual product can then be easily removed from the oral cavity. The Cephalon product is a tablet that is placed between the gums and the buccal mucosa, where it effervesces upon contact with moisture and gradually disintegrates over 5 to 40 minutes in most cases. Once placed in the buccal area, it is possible to remove the remaining product from the oral cavity; however, it is not as easily retrieved as the Actiq lozenge on a stick. Nevertheless, residual drug is swallowed and undergoes extensive first pass metabolism. Cephalon, Inc. also holds the NDA for Actiq. However, the current application has been filed under Section 505(b)(2) of the FD&C Act, as the sponsor has referenced the Actiq approval. The Actiq approval fell under Section 505(b)(2) as that application referenced the approval for NDA 16-619 for Sublimaze, fentanyl injectable, which remains proprietary to a different sponsor. There are no outstanding patents on Sublimaze.

The CMC section of this application was reviewed by Jila H. Boal, Ph.D. The Clinical Pharmacology and Biopharmaceutics section was reviewed by Chandra S. Chaurasia, Ph.D. The Pharmacology and Toxicology review was completed by L.S. Leshin, D.V.M., Ph.D. The clinical safety and efficacy review was completed by Robert B. Shibuya, M.D. A statistical review and evaluation was completed by Yongman Kim, Ph.D. Consultation on this application was obtained from the Controlled Substances Staff, the Office of Surveillance and Epidemiology, and the Division of Drug Marketing, Advertisement and Communications.

The sponsor submitted a single, adequate and well-controlled trial in support of the efficacy of their product. The need for only one trial was agreed upon with the Division during product development, based on the extensive information known about the drug substance and on the similarity of the product to the Reference Listed Drug (RLD), Actiq. The critical matters to be elucidated in studies of this product were whether the new formulation works as effectively as the RLD, the pharmacokinetic profile of the formulation, and whether new safety concerns are raised that are formulation specific.

Efficacy:

Study 099-14 was modeled on the critical trial submitted to support the Actiq approval. Cancer patients experiencing 1 to 4 episodes per day of breakthrough pain, despite treatment with around-the-clock potent opioids, were titrated in an open-label phase to a dose of study drug that provided a reasonable balance of effectiveness and tolerability. The patients were then dispensed 10 sequential doses, 7 of which were active drug and 3 of which were placebo. The placebo doses were scattered among the active doses, with randomization restricted to 18 sequences defined by the protocol. Pain scores were recorded before and after each dose. If treatment of a breakthrough pain episode was ineffective after 30 minutes, patients were permitted to use their regular rescue immediate-release opioid medication.

The primary outcome assessment was Pain Intensity (PI) measured with an eleven-point numerical rating scale. The outcome was analyzed by using a Summed Pain Intensity Difference from pre-dose to 15 and 30 minutes post-dose (SPID30). The SPID30 was calculated as follows:

$$[PI (\text{pre-dose}) - PI (15 \text{ minutes post-dose})] + [PI (\text{pre-dose}) - PI (30 \text{ minutes post-dose})]$$

Missing data within a given episode of breakthrough pain were imputed using the Last Observation Carried Forward methodology.

Secondary outcome measures were:

- Pain Intensity Difference for each dose

- Pain Relief after each dose
- Total Pain Relief, defined as the sum of the Pain Relief scores at 15 and 30 minutes post-dose
- Global Medication Performance assessments at 30- and 60-minutes post-dose
- Comparison of rescue medication use after study drug vs. placebo doses
- Comparison of time from dosing to use of rescue medication after study drug vs. placebo doses

Of the 123 subjects who entered the open-label phase of the study, 77 were successfully titrated and entered the double-blind phase. Sixty-eight subjects completed the study. Seventy-two subjects were evaluated as the ITT population, defined as those patients who had at least one episode of breakthrough pain treated with placebo and one episode treated with active drug, and for whom each of these episodes had adequate data recorded. Of note, 13 subjects were enrolled despite their not meeting the minimum daily opioid requirement of 60 mg of morphine per day (or equianalgesic/equipotent doses of another opioid). These subjects, on doses from 5 to 45 mg of morphine equivalents per day, appeared to tolerate treatment with study drug nonetheless. Only one of these subjects discontinued from the study due to an adverse event (constipation).

The results of the primary efficacy analysis documented a statistically significant treatment effect for the active drug product. Due to the fact that the 18 sequences of drug and placebo were not completely random as, per protocol, the first dose could not be placebo and placebo could not be dosed consecutively, the sponsor included a permutation test in their analysis at the request of the Division. Dr. Kim's Table 3 summarizes the results of the primary analysis and is reproduced below:

**Table 1. Sponsor Analysis of Primary Efficacy Variable for Study 099-14: SPID₃₀
(Full Analysis Population)**

SPID ₃₀	OVF (N=72)	PLACEBO (N=72)	P-VALUE
LSMean (SE)	3.0 (.12)	1.8 (.18)	<.0001*
Permutation Test			<.0004**

Note: Treatment group was defined as 'as-treated' for each episode.

* P-value based on ANOVA with terms for treatment, site as fixed effects and subject as random effect.

** P-value of permutation test based on 10,000 re-randomizations.

Sensitivity analyses performed by Dr Kim resulted in findings that were similar to the sponsor's primary analysis. The results of the secondary outcome analyses were generally supportive of the primary outcome results.

Dr. Shibuya employed a sensitivity analysis published in an article by Farrar et al¹. In that article, Farrar examined the data from the critical Actiq trial using a series of analyses, and presented optimal cutoff values for determining clinical significance in acute pain trials based upon the results of these six analyses. Dr. Shibuya evaluated the data from this trial and found that the results met five of the six Farrar criteria.

Clinical Safety:

The evaluation of the safety database for this application is limited by a number of factors:

- Patients were on background treatment with potent opioids
- Patients were allowed to use immediate-release opioids for rescue

¹ Farrar, JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88;287-294.

- The within-subject, cross-over design allows for carryover effects
- In most cases, the exact time of an adverse event in relation to dosing with active drug or placebo was not captured.
- Approximately half of the subjects had advanced malignancies, and many also had comorbid conditions, which led to a large number of deaths and serious adverse events that could not always be clearly distinguished from drug effects.
- Many of the patients were also being treated with other highly toxic drugs.

A total of 710 subjects comprised the safety database, most of these patients having been treated in open-label safety studies². Fifty-three subjects died. Dr. Shibuya has carefully evaluated each of these cases and concluded that causality cannot be clearly attributed to study drug exposure in even a single case. Note that a spouse of a subject did die of an overdose (see below).

There were 278 reported serious adverse events in 78 discrete subjects. Again, Dr. Shibuya has carefully reviewed each and every case. He concluded that the vast majority of the events were related to either worsening of or complications due to the underlying malignancy, or were unrelated to either the malignancy, treatment of the malignancy, or study drug exposure, e.g., coronary artery disease.

The most common adverse events were nausea, dizziness, vomiting, fatigue, constipation and somnolence. Seventy-one subjects experienced application site reactions, ranging from site irritation to ulcer, paresthesia, pain, vesicles and bleeding. Twelve subjects discontinued due to application site reactions and 2 subjects had reactions that resolved, but with "residual effect." These events often occurred after short-term exposure (69% during titration) and 25% of the events lasted for 8 to 30 days. None of the events met the definition of "serious," and only 3% were described as "severe." The most common of the application site reactions were pain, ulcer and irritation.

At the Division's request, the sponsor undertook a small study to assess the safety of their product in patients with mucositis. In this single-dose (200 mcg), open-label study, 16 patients (8 with mucositis and 8 without mucositis) were evaluated. The mean AUC₀₋₈ was approximately 30% higher in the patients with mucositis. Dr. Shibuya found no increased systemic or local toxicity in the mucositis patients in this study or in the few patients with mucositis found in the rest of the safety database.

There were four cases of medically important respiratory depression related to study drug exposure. For two patients, study drug was part of a polydrug overdose. Both of those

² Patients from the sponsor's studies of breakthrough pain in non-cancer chronic pain patients, were included in the safety database.

patients had histories of suicide attempts. One patient's spouse, who apparently pilfered the patient's study drug and self-administered it, died due to respiratory failure. One patient used an incorrect and much higher dose than he had been prescribed during the titration period and required resuscitation.

Nonclinical Safety:

As per Dr. Leshin's review, there is one impurity in the drug substance, that exceeds the ICH threshold for qualification and which has not been tested for genetic toxicity. However, as this impurity does not contain a structural alert for mutagenicity, and as it has a similar pharmacodynamic and toxicologic profile as fentanyl and has been the current specification of — does not raise significant safety concerns. I agree with Dr. Leshin's conclusion and his recommendation that the sponsor either reduce the specification or provide adequate qualification as soon as possible.

Clinical Pharmacology and Biopharmaceutics:

A particular concern in regard to the safe use of FENTORA is its higher bioavailability compared to Actiq. As there is a high likelihood that some patients will be converted from Actiq to FENTORA during the course of their disease, the clinical pharmacology team and the clinical team performed a careful comparative evaluation of the pharmacokinetics of the two products. As per Dr. Chaurasia's review, the fraction of FENTORA that is absorbed transmucosally is approximately 50% of the total dose, compared to 25% for Actiq, resulting in absolute bioavailabilities of $65\% \pm 20\%$ and $47\% \pm 11\%$ for FENTORA and Actiq, respectively. Thus, an approximately 30% lower dose of FENTORA will achieve a systemic exposure comparable to the administration of any particular dose of Actiq.

The sponsor has provided a dose conversion table in the Dosing and Administration section of the package insert that provides conservative guidelines for switching patients from Actiq to FENTORA. Additionally, precautions and warnings in the product labeling and RiskMaP also address proper dosing and monitoring during conversion.

Chemistry, Manufacturing and Controls:

After extensive discussions between the Agency and Cephalon, it was agreed that all of the tablets may be white in color, with a single-digit, embossed numeral to distinguish the different doses. We concluded that this plan would be satisfactory from a risk management perspective. While this may not be the ideal method for reducing the risk of accidental ingestion of an incorrect dose, there were a number of legitimate reasons for choosing this path. The particular formulation that provides the effervescence and

relatively fast breakdown of the product, also results in

1. Thus, it is difficult at best to either emboss a full dose on the tablets or to provide color — that clearly distinguishes between the tablets. However, the tablets will remain within the color-coded (by dose) blister package until use and, the label clearly states that only one dose should be in a patient's home at any time. As patients titrate to their initial stable dose or change dose over time, they will be instructed to use multiples of a single dose-strength, and to discard any remaining tablets from a previous dose-strength when they are prescribed a new dose-strength.

Risk Management:

Fentanyl is a potent opioid and even in legitimate, opioid-tolerant patients who are prescribed fentanyl products for the treatment of pain, the risk of overdose due to misuse or inappropriate prescribing is significant. In addition, this product is highly desired by addicts and others who abuse opioid drugs. As such, and in spite of the fact that FENTORA will be a Schedule II controlled substance, (the most stringent level of control under the Controlled Substances Act), it is essential that a carefully designed Risk Minimization Action Plan (RiskMaP) be in place at the time of product approval. In conjunction with the Controlled Substances Staff and the Office of Surveillance and Epidemiology, the Division has worked closely with the sponsor to develop a RiskMaP that is designed to address the problems that may occur due to misuse and accidental exposure by children, pets and other non-patients, and to promote legitimate patient use.

The sponsor's proposed RiskMaP addresses misuse and accidental exposure, via: extensive warnings and dosing instructions (including recommendations regarding conversion from Actiq to FENTORA) in the patient package insert; a MedGuide to alert patients to the potential problems associated with the product; carefully designed product packaging that includes warnings for patients and caregivers and "check lists" for pharmacists; educational programs for patients, pharmacists, caretakers, prescribers and other health care providers; surveillance for both diversion and abuse, and for misuse, overdose and other pertinent adverse events; and interventional strategies that will be employed when these types of problems are documented. (See Dr. Shibuya's summary of the RiskMaP)

The sponsor's RiskMaP remains incomplete, however. The required elements for this RiskMaP are:

1. Implementation of a program and distribution of materials to educate prescribers, pharmacies, nurses, and patients about the risks and benefits of FENTORA.
2. Implementation of a reporting and data collection system for safety surveillance.

3. Implementation of a plan to monitor, evaluate, and determine the incidence of use of FENTORA by opioid nontolerant individuals, misuse of FENTORA, and unintended (accidental) exposure to FENTORA.
4. Implementation of improvements in educational components or other interventions as needed if monitoring reveals evidence of failure to adequately convey the key safety messages of the RiskMAP.

The sponsor has yet to provide the Agency a complete RiskMap with comprehensive details of their plan to meet the required elements. Therefore, the Agency cannot assess whether the required elements have been met. As the safe use of FENTORA is dependent upon an agreed upon RiskMaP that has received a thorough review by the Agency, we are unable to finalize our determination regarding approvability of the product at this time.

The Controlled Substances Staff has expressed additional concerns and made additional recommendations to address the potential for abuse and misuse in their reviews. Dr. Shibuya has carefully addressed each of these concerns and recommendations in his review, and has concluded that they are not relevant to the product. I concur with his conclusions.

Discussion

The sponsor has submitted an application that clearly demonstrates the efficacy and safety of FENTORA when it is used according to the agreed upon labeling and the proposed RiskMaP. However, at this time, the proposed RiskMaP has not been finalized due to details that are still under development by the sponsor and that have not received final review by the Agency.

There are significant dangers and safety concerns that are inherent with any potent-opioid drug product. However, these dangers and concerns must be weighed against the value of the product for the intended patient population. Breakthrough cancer pain is a devastating condition that is often unresponsive to the available approved analgesic products. While FENTORA does not appear to provide an advance in the treatment of breakthrough cancer pain compared to Actiq, it is highly effective in that patient population. FENTORA's potentially more rapid onset of analgesia compared to Actiq is mitigated by some of its inherent risks, such as the potential for confusion regarding dose when converting from Actiq, the fact that it is more likely to be entirely consumed before appropriate intervention is possible when compared to Actiq, an increase in available fentanyl for non-legitimate users, and the possibility of inadvertent and potentially lethal exposure to children and other non-patients. It is, however, less likely than Actiq to be mistaken for candy by a child; and, the fact that residual product will likely remain in the oral cavity even after partial use provides an additional safety factor in regard to inadvertent exposure by children, pets and other non-patients.

No risk management techniques can completely eliminate the misuse of opioid drug products. Nevertheless, FENTORA is a safe and effective product when used according to labeling, and the risks associated with its approval can and will be addressed by carefully crafted product labeling and an approved RiskMaP. The studies provided in support of this NDA, and our experience with other potent-opioid drug products, indicate that misuse and prescribing errors can potentially be minimized by well-delineated instructions for use, appropriate warnings, and careful surveillance for abuse, diversion and misuse, as well as for deaths, overdoses and pertinent adverse events. The sponsor has worked diligently with the Agency to develop a risk management program that will address these concerns, and any problems that do develop should become apparent early on, based on the surveillance plan that has been incorporated into this program. However, the RiskMaP will require further development and review before this application can be approved.

Action recommended by the Division: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
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Addendum to Clinical Review: RiskMAP, Consultants' Responses, and Labeling

NDA #:	21-947
Drug Name (generic):	<i>FENTORA</i> (fentanyl buccal tablets)
Sponsor:	Cephalon
Indication:	Management of breakthrough pain in opioid-tolerant cancer patients
Type of Submission:	NDA submission and responses to information requests
Date of Review:	June 27, 2006
Reviewer:	Robert B. Shibuya, M.D.
Project Manager:	Kimberly Compton, R.Ph.

This document will serve to update the Clinical Review of NDA dated April 28, 2006 with regard to the Risk Minimization Action Plan (RiskMAP) and labeling and describe how advice from the Office of Surveillance and Epidemiology (OSE), Controlled Substances Staff (CSS), and the Division of Drug Marketing, Advertising, and Communication (DDMAC) was incorporated. Because the issues of labeling and RiskMAP were closely related, most of the internal meetings and teleconferences with the Applicant covered both topics. OSE participated in all internal meetings and teleconferences. CSS participated in most of the internal meetings and most of the teleconferences. DDMAC participated in two internal labeling meetings.

The tradename "*FENTORA*" and generic name "fentanyl buccal tablets" have been found to be acceptable. The remainder of this review will use the acronym "FBT" to reference the product.

Chronology:

<u>Submission, Agency Response, Meeting, or Teleconference</u>	<u>Date</u>
Initial package insert, Medication Guide, and RiskMAP submitted	8/31/05
OSE consult received by DAARP	4/20/06
CSS Executive Summary received by DAARP	5/9/06
Teleconference with Applicant	5/18/06
Discipline Letter to Applicant with RiskMAP comments	5/22/06
DDMAC consult received by DAARP	5/25/06
Internal RiskMAP meeting	6/1/06
Internal RiskMAP meeting	6/5/06
Internal labeling and RiskMAP meeting	6/8/06
Internal labeling and RiskMAP meeting	6/15/06
Applicant's response to Discipline Letter and teleconferences*	6/16/06

<u>Submission, Agency Response, Meeting, or Teleconference</u>	<u>Date</u>
Internal labeling and RiskMAP meetings/teleconference with Applicant	6/23/06

*Applicant submitted several versions of the packaging and comments regarding the RiskMAP that are not currently appearing in the Electronic Document Room

Major RiskMAP Issues and Resolution:

As described in the Clinical Review, the OSE and CSS consults identified several issues that were discussed with the Applicant over the course of approximately 6 weeks. The major issues to be surmounted and the resolution are summarized in the table following:

<u>Issue</u>	<u>Resolution</u>
Potential for accidental pediatric exposure	Prominent warnings added to labeling, including cartons.
	/ / /
Risk of medication errors	
FBT is more bioavailable than ACTIQ	Warning added to Black Box and discussed in pertinent sections of package insert.
The conversion scheme from ACTIQ to FBT is unnecessarily complex	Scheme simplified within the context of the safety and pharmacokinetic data.
Tablet colors may cause confusion.	All tablets to be white in color with the first numeral of the strength debossed. A distinctive color scheme of the packaging is to be used as a secondary aid to identify strength.
The container color scheme may cause confusion.	Each strength has a distinctive color used in both blisters and cartons.
FBT should have a Medication Guide.	Medication Guide submitted, negotiated, and found acceptable.
Educational Plan: Prescribers and patients must understand that ACTIQ and FBT are not interchangeable.	Surveys to determine whether prescribers, pharmacists, and patients understand the key warnings found acceptable by OSE.
Pharmacovigilance	
Report deaths, peds exposures, medication errors as 15-day alerts.	Applicant verbally agreed.
Update RiskMAP activities with Quarterly Reports.	Applicant agreed.
Improve survey methodology.	Surveys modified and acceptable.
Make abuse/diversion warnings more prominent.	Language added to Black Box Warning.

<u>Issue</u>	<u>Resolution</u>
Minimize risk of overdose during titration.	Package insert instructs to prescribe/dispense only one strength during titration. Pharmacokinetic data supports use of up to four x 100 mcg tablets simultaneously.

Major Labeling Issues and Resolution:

Input from Chemistry, Pharm/Tox, Clinical Pharmacology, OSE, CSS, and DDMAC was incorporated into the labeling negotiations. Input from OSE and CSS was summarized in the main Clinical Review for this NDA. Briefly, DDMAC noted that the _____ was promotional. DDMAC also noted that the applicant _____, noted some inconsistencies between the original proposed label and that of ACTIQ, and has several comments that clarified the label. Key issues and the corresponding resolution are summarized below.

<u>Section of Package Insert</u>	<u>Resolution</u>
Generic Name	The term "effervescent" was not compatible with the CDER Data Standards Manual and the Nomenclature Committee did not agree with the Applicant's position that "effervescent" was educational. The final generic name for this product is "fentanyl buccal tablet"
Black Box Warning	Additional warnings were added regarding abuse liability, the higher bioavailability compared to ACTIQ, rendering a mcg to mcg substitution inadvisable, and limiting the prescriber base.
Description	Language _____ were removed along with claims that were speculative.
Clinical Pharmacology	The Clinical Pharmacology section was extensively edited to make it consistent with other recently approved opioids, particularly those containing fentanyl. The positioning of the tables (comparison to ACTIQ and dose proportionality) and figures were rearranged. Results from Study 16 (mucositis) were added.
Clinical Trials	The figure showing _____ was substituted with a figure showing pain intensity difference curves.
Indications and usage	Additional warnings regarding opioid-naive patients and indicating the appropriate prescriber base were added.

<u>Section of Package Insert</u>	<u>Resolution</u>
Precautions	A section regarding application site reactions was added. The review team felt that the incidence (10%) in the total safety population (cancer and non-cancer patients) was appropriate. The incidence in the cancer-only population was 8%.
Drug Interactions	Additional information regarding CYP 3A4 inhibitors was added.
Carcinogenicity/Pregnancy/L&D/Nursing	Slight modifications were made to reflect what information the applicant had right-of-reference or whether data were available.
Adverse Reactions	Additional data from 120-day safety update added. At the Division's request, data for Tables 4 & 5 was requested for cutoffs of cutoffs yielded cumbersome tables so the 5% cutoff was used. American English terms replaced the _____, used in the original label. The review team felt that data from the cancer population was appropriate for this section.
Dosage and Administration	Additional language regarding patients with hepatic/renal impairment, mucositis, or on CYP inhibitors added. Table 6 (conversion from ACTIQ) simplified. Warning to prescribers to only prescribe one strength at a time was added.
How Supplied	Modifications were made to reflect the fact that all tablets are debossed and white and to describe the color scheme of the packaging.

With regard to the Medication Guide, the following major revisions were made:

- The "most important information" section was simplified to the key messages (opioid-tolerant patients only, use exactly as directed, FBT is different from ACTIQ).
- Key safety messages are now bolded throughout the document and some of the language was clarified.
- Abusability messages more prominent.

Post-Marketing Agreements:

1. Drs. Harapanhali and Boal indicated that Cephalon would have to agree to two conditions.
 - a) Provide confirmation that the manufacturing process and controls for white tablets of all strengths are the same as for the white 200 mcg tablets described in the NDA and to provide stability data for the white tablets.
 - b) Reduce the specification for the μ impurity in the active drug substance to NMT μ by the end of December 2006.

Reviewer's Recommendation:

The applicant has adequately addressed the Risk Minimization issues and acceptable labeling has been negotiated. The reviewer recommends that FBT be approved for all proposed strengths (including 800 mcg).

Robert B. Shibuya, M.D., Medical Officer

CC: Original IND, HFD-170 Division File, B. Rappaport, S. Hertz, R. Shibuya, K. Compton

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/s/

Robert Shibuya
6/28/2006 11:51:46 AM
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Sharon Hertz
6/28/2006 06:54:06 PM
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I concur with Dr. Shibuya's conclusions.

CLINICAL REVIEW

Application Type NDA 21-947
Submission Number 000
Submission Code

Letter Date 31 August 2005
Stamp Date 2 September 2005
PDUFA Goal Date June 30, 2006

Reviewer Name Robert B. Shibuya, M.D.
Review Completion Date 28 April 2006

Established Name Fentanyl effervescent buccal tablet
(Proposed) Trade Name To be determined
Therapeutic Class Opioid analgesic
Applicant Cephalon

Priority Designation Standard

Formulation Oral transmucosal tablet
Dosing Regimen PRN
Indication Breakthrough pain in opioid
tolerant cancer patients
Intended Population Opioid tolerant cancer patients

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Clinical Review
Robert B. Shibuya, M.D.
NDA 21-947 (000)
TRADE NAME (Fentanyl buccal tablets)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The data submitted in this application are sufficient to support a finding of efficacy and safety for OraVescent Fentanyl for the proposed indication (management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain).

This 505(b)(2) new drug application for OraVescent Fentanyl (OVF) rests, in part, on the Agency's previous findings of safety and efficacy for the fentanyl moiety which was originally approved in 1968. In addition to the Agency's knowledge of fentanyl as a potent analgesic in the surgical and perioperative setting, chronic pain, and breakthrough pain in cancer, the applicant has submitted data from one adequate and well controlled study, several clinical pharmacology studies, and uncontrolled, open-label safety data on approximately 600 additional patients.

The adequate and well controlled study submitted provides substantial evidence of effectiveness. The safety data submitted were limited for several reasons including:

1. Effectively, there was no comparator group. Because of the nature of breakthrough pain, the placebo-controlled study was of a cross-over design, not a parallel group design. Patients were dispensed 10 doses of study drug, seven of which contained fentanyl; three of which were placebo. Since patients may have self-administered several doses in a day, it was difficult to attribute adverse events to OVF definitively.
2. Patients were already on around-the-clock opioid. The study drug was additional opioid dosed over the background opioid.
3. Approximately half of the safety database was comprised of patients with advanced malignancies where therapies for the malignancy, along with treatments for other comorbidities, were co-administered.

In the context of these limitations, the available safety data were carefully reviewed. Not unexpectedly, OVF could be associated with typical opioid-related adverse events, many of which resulted in discontinuation of the drug. The adverse events that appeared specific to this formulation were complaints pertaining to the application site. These were as minor as paresthesia and as severe as ulceration and bleeding. These adverse events appeared to be self-limited but took up to one month to resolve. The application site abnormalities were found in the non-cancer population, where the oral mucosa would be expected to be robust as well as the cancer patient population, where the oral mucosa would be expected to be more delicate.

The study designs of the adequate and well controlled study and the open-label safety studies, in concert with the pharmacokinetic data, support the sponsor's proposed dose finding regimen and redosing information.

1.3 Summary of Clinical Findings

Oravescent fentanyl is a reformulation of fentanyl for oral transmucosal administration. Fentanyl is a potent mu-opioid agonist and is approved in parenteral, extended-release transdermal, and oral transmucosal formulations.

The approved oral transmucosal formulation, Actiq®, reaches a peak plasma concentration in between 45 and 90 minutes. Since breakthrough pain in cancer is typically sudden in onset and builds quickly to a crescendo, a formulation that is absorbed more quickly is desirable. Oravescent fentanyl was developed with this in mind. Theoretically, this formulation enhances absorption by controlling the local pH, opening tight junctions, and inducing solvent drag. This reviewer notes that the clinical pharmacology data do not consistently support the assertion that

1.3.1 Brief Overview of Clinical Program

The applicant has submitted two trade names _____ both of which were rejected by DMETS and proposes a generic name of “fentanyl effervescent buccal tablets.” Previous submissions however, refer to the product as “Oravescent Fentanyl.” Since an acceptable trade name has not been identified and fentanyl effervescent buccal tablets is under review, for the purpose of continuity, this product will be identified as Oravescent Fentanyl (OVF) in this review.

OVF is a reformulation of fentanyl citrate for oral transmucosal administration. The applicant seeks an indication of the treatment of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy.

As a reformulation of a well-characterized chemical moiety where there is already an approved product (Actiq®) using the proposed route of administration, the clinical development program has been modest (four studies). The applicant has conducted one (123 patients screened, 68 patients completed) adequate and well-controlled study to support a finding of efficacy and safety. To further augment the safety database, the sponsor has submitted interim data for a second adequate and well-controlled study (71 patients screened, 47 patients completed); an open-label, long-term safety study in patients with cancer (208* patients); and an open-label, long-term safety study in patients with pain not due to malignancy (406 patients).

*Two patients who rolled over from the adequate and well-controlled trials were retitrated

With the exception of the healthy volunteer (clinical pharmacology) trials, the applicant has studied opioid-tolerant adult patients with breakthrough pain in the setting of chronic pain consequent to malignancy or of non-malignant etiologies. The applicant has attempted to follow patients for longer than 12 months and a small number of patients have reached that duration of treatment. However the majority of the patients comprising the safety database (containing 710 patients) were treated for less than 6 months duration. OVF is not marketed anywhere in the world so there is no foreign postmarketing safety data to consider.

1.3.2 Efficacy

The applicant submitted a single adequate and well-controlled study to support a finding of efficacy for OVF. This study (protocol 099-14) enrolled patients with chronic pain due to malignancy who were currently treated with an around-the-clock (ATC) opioid regimen but were experiencing 1-4 episodes of breakthrough pain per day. The study consisted of two parts, an open-label titration phase and the double-blind phase which was a ten-period crossover design. During the open-label phase, patients were titrated to a dose where a single tablet successfully treated an episode of breakthrough pain without unacceptable side effects. Following the titration to a successful dose, patients were dispensed 10 sequential, numbered doses. This regimen could have been one of 18 possible sequences where 7 of the doses were OVF at the successful dose and 3 of the doses were placebo. The placebo doses were scattered within OVF doses randomly*. With each episode of breakthrough pain, patients were to take the next dose in sequence and record pain intensity, pain relief, information about the use of unblinded rescue medication, and provide a global assessment of study drug.

*The 18 possible sequences were nonrandom in that the first dose during double-blind could not be placebo, nor could placebo be dosed consecutively. At the request of the Division, the sponsor's analysis included a permutation test to address the non-randomness introduced by these restrictions of possible sequences.

From a statistical perspective, the study showed a statistically significant treatment effect for the primary efficacy endpoint [summed pain intensity difference over 30 minutes (SPID₃₀)] with a p-value < 0.0001. With the exception of one secondary endpoint (interval between study drug and rescue) the study showed statistical significance for all of the secondary endpoints (p-values ranging from < 0.0001 to 0.005). The permutation test showed no effect of the limitations to the randomness of the sequence of treatments administered.

While the study showed a statistically significant treatment effect, the mean difference in the SPID₃₀ was not impressive (3.2 to 2.0). Therefore, the results of the study were subjected to the six criteria found to be useful for determining clinical significance in an analgesic trial (Farrar et al¹). The trial met 5/6 of these criteria. Therefore, in this reviewer's opinion, the study demonstrated substantial evidence of efficacy in this population.

Limitations of this study design include the short duration of the double-blind evaluation (typically less than one week) and the enrichment design. However, given that fentanyl's analgesic efficacy is known, the overall health of the patient population, and tightly circumscribed nature of the indication, this design is felt to be adequate by the Division.

1.3.3 Safety

The evaluation of safety for OVF is limited for various reasons.

1. In the patient population studied, the fentanyl moiety is being dosed against a background of around-the-clock opioid which could be fentanyl itself. Fentanyl, being a mu-opioid agonist, has the adverse event profile characteristic of all opioids (sedation, respiratory depression, nausea, vomiting, constipation, etc). Chest wall tightness, the one fairly specific adverse event characteristic of fentanyl, is typically only seen at anesthetic doses

in opioid-naive patients. Thus, it is difficult, if not impossible, to attribute a typical opioid adverse event to OVF and not the ATC opioid.

2. The placebo-controlled trials were of a crossover design where placebo was essentially alternated with OVF.

Therefore, to assess causality, the precise relationship between the timing of the dose and onset of the adverse event would have to be known. Unfortunately, in most cases, the exact time of the onset of the adverse event was not captured. Specifically, for the serious adverse events, in only 34 of the 278 (12%) incidents was the time of onset documented. Furthermore, for the majority of the duration of the open-label studies, the time of dosing was not documented. To simplify the recordkeeping for the patients, the diary was changed so that patients only recorded the number of breakthrough pain episodes and tablets taken each day but did not note the time of each tablet.

Many patients self-administered more than one dose of OVF or placebo per day. Therefore, there is no clear placebo group to make a comparison of the safety data.

3. Approximately half of the patients comprising the safety database had advanced malignancy and many had a number of other comorbid conditions which led to a large number of deaths, serious adverse events, and other safety findings that were not likely to be due to OVF. Furthermore, these patients may have been being treated with cytotoxic chemotherapy, radiation, or hormonal therapies for the malignancy and other pharmacologic agents for comorbidities.

The safety database comprised a total of 710 patients, a small percentage of whom were administered OVF for over 12 months. Most of the safety database consists of data from open-label safety studies (Protocols 099-15 and 3040).

In the OVF trials, all spontaneously reported, solicited, or observed adverse events were recorded on the Case Report form. To further augment documentation of adverse events, the sponsor included a "Side Effects Diary" for Studies 14 and 15. The sponsor also used a Serious Adverse Event reporting sheet which contained additional information on the SAEs. Because of the complex clinical scenarios in which treatment emergent adverse events occurred, adverse events were attributed to study drug except where noted following.

The overall mortality rate was high (7%) with 53 of the 710 patients in the safety database dying. This is to be expected in a population with a substantial proportion of patients with advanced malignancies. Information contained in narratives, case report forms, and additional documentation (where appropriate) was carefully reviewed. Given the limitations inherent in interpreting this database, in none of the 53 cases of death could the inciting episode or death itself be attributed to OVF.

Serious adverse events were numerous as well [278 incidents (deaths and non-fatal SAEs)] which were reported by 78 discrete patients who did not die while on study. Again, the available information was reviewed with care. Excepting the cases of overdose (see Section 7.1.4) and

these four patients: [pneumonia and confusional state (1 patient), syncope (1 patient), neurogenic bladder (1 patient), and seizure (1 patient most likely seized due to chronic meperidine administration but the role of OVF could not be ruled out)], the SAEs appeared to be due to worsening of the underlying disease (such as direct extension of the primary tumor or metastases), a complication of the malignancy (such as pancytopenia), or unrelated to the malignancy and OVF (such as coronary artery disease). For the cases where the SAE might possibly be related to OVF, the prevalence of the event does not exceed that can be expected for this patient population.

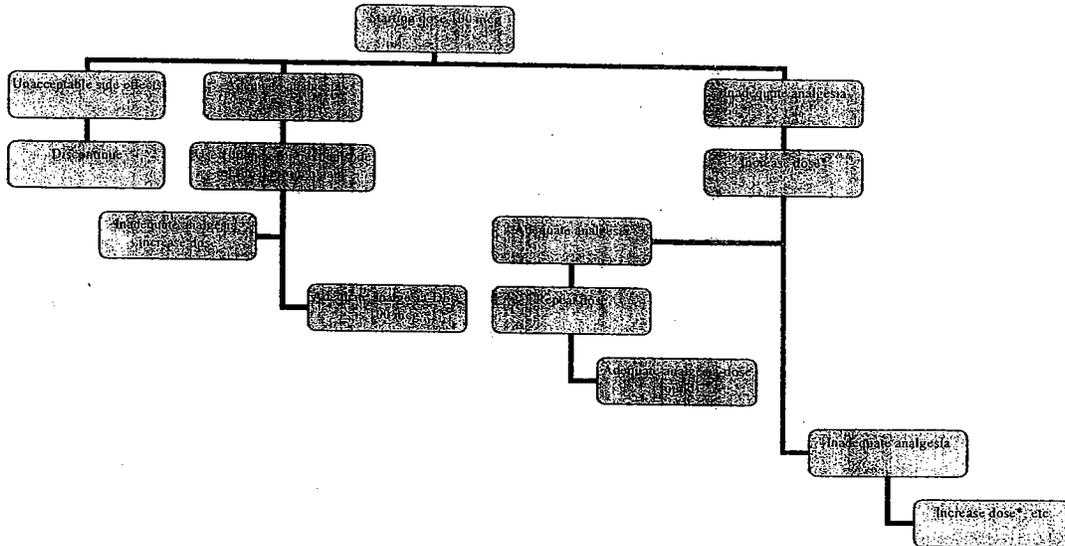
The most common adverse reactions were typical opioid side effects: nausea, dizziness, vomiting, fatigue, constipation, and somnolence. Sixty-four patients discontinued prematurely due to non-serious adverse events. The incidence of treatment emergent adverse events was 75% for the cancer population and 71% in the non-cancer population. A substantial proportion of patients experienced adverse events pertaining to the application site of the drug.

The overall safety profile for OVF appears typical for a potent opioid. There were four incidents of medically significant respiratory depression related to the use of OVF (see Section 7.1.4). One was in a patient with a history of suicide who experienced a polydrug overdose, one was an overdose, one was the spouse of a patient who may have pilfered OVF and self-administered it, and one occurred in a patient during the titration phase who was confused with regard to which strength of tablet he should use. The last case will impact how the drug will be dispensed during titration.

1.3.4 Dosing Regimen and Administration

The applicant has determined the scheme for finding the appropriate dose of OVF. The algorithm for dose finding follows.

Figure 1: Dose Finding/Titration Algorithm Used In Clinical Trials Of OVF



Best Possible Copy

*Doses to be used are 100 => 200 => 400 => 600 => 800 mcg

This method of finding the dose de novo was used in all clinical trials and appears to have been successful in determining whether OVF would be tolerated in an individual and, if tolerated, finding the appropriate strength. For patients converting from Actiq®, the applicant proposes to use $\leq 50\%$ of the current dose of Actiq®. The conversion scheme was tested in Study 15. Given the relative bioavailability between OVF and Actiq®, the proposed conversion scheme appears acceptable from a safety perspective even though it is unnecessarily complex (see section 8.7).

The applicant proposes as needed (prn) dosing with a provision to redose (with the prescribed strength) after 30 minutes if analgesia is inadequate following the first dose. This redosing regimen was studied in Studies 15 and 3040, the open-label safety studies.

1.3.5 Drug-Drug Interactions (from Dr. Chaurasia's review)

Fentanyl is metabolized in the liver and intestinal mucosa to norfentanyl by cytochrome P450 3A4. Inhibitors or inducers of 3A4 may affect the pharmacokinetics of OVF. A clinical pharmacology study included the effect of pretreatment with ritonavir which resulted in a 174% increase in the AUC for a single IV dose of fentanyl. In light of the wide variety of 3A4 inhibitors, for patients on concomitant 3A4 inhibitors, dose adjustments should be made with caution and monitoring should continue for an extended period of time.

1.3.6 Special Populations

OVF was not studied in special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

OraVescent fentanyl (OVF) is a tablet containing fentanyl citrate as the active ingredient in a matrix that controls the pH of the buccal mucosa that it contacts and effervesces as it dissolves over the period of 5-40 minutes. The applicant proposes a generic name of "fentanyl effervescent buccal tablet" and has not yet proposed an acceptable trade name. In previous submissions to IND 65,447, the product was identified as "OraVescent Fentanyl (OVF)." For the purpose of continuity, this review will use the name and abbreviation OraVescent Fentanyl (OVF).

Fentanyl is an opioid analgesic that was originally approved in 1968. OVF represents a new formulation. The applicant proposes an indication of the treatment of the management of breakthrough pain in patients with cancer who are already receiving and are tolerant to opioid therapy for their underlying persistent pain. The product is intended for use in adults and the proposed labeling contains a standard warning that the safety and efficacy of the product have not been studied in the pediatric population.

2.2 Currently Available Treatment for Indications

The current treatment paradigm for breakthrough pain in the setting of chronic pain due to malignancy is to treat the episode with a short-acting, immediate-release oral opioid (or opioid/non-opioid combination product) consisting of approximately 15% of the patient's total baseline opioid dose. The preparation of opioid tends to be an immediate-release solid oral dosage form, typically morphine, hydromorphone, or oxycodone. None of the immediate-release oral opioids are approved for this specific indication.

Actiq®, a lozenge formulation of fentanyl citrate for oral transmucosal administration, was approved in November 1998 for the indication of breakthrough pain in patients with persistent cancer pain. Actiq® had theoretical advantages over the existing immediate-release solid oral dosage forms for this indication. First, fentanyl is a potent opioid with a rapid onset of effect (minutes) and short duration of action (usually dosed parenterally every 1-2 hours). This pharmacodynamic profile is complementary to breakthrough pain episodes which tend to be severe in intensity but short in duration. However, fentanyl is not an acceptable candidate for standard oral administration due to high first-pass metabolism. Actiq® addressed the problems of first-pass metabolism and achieving therapeutic plasma levels relatively quickly without parenteral administration by using the oral transmucosal route. Fentanyl is highly lipophilic and easily passages the oral mucous membrane. Actiq® is applied to the buccal mucosa where the active moiety enters the bloodstream directly from the capillaries underlying the oral mucosa.

2.3 Availability of Proposed Active Ingredient in the United States

In the United States, the fentanyl moiety is approved in three other products (not including generic forms). Table 1, following, summarizes the highlights of the regulatory and marketing experience.

Table 1: Pertinent Facts Regarding Currently Marketed Fentanyl Containing Products.

Trade name/description	NDA	Approval Date	Major Labeling Changes	Major Safety Concerns
Sublimaze® (fentanyl injection)	16-619	19 February 1968	None	Typical opioid adverse events (sedation, respiratory depression, nausea, vomiting)
Duragesic® (fentanyl, extended-release, transdermal)	19-813	7 August 1990	None	<ol style="list-style-type: none"> 1. Typical opioid adverse events (including constipation due to the chronic nature of use). 2. Currently, the safety of this product (and its generics) is being evaluated in two specific areas: patch non-adhesion and the use of occlusive overlays. These concerns are specific to the dosage form. 3. Since this product is used in outpatients, there are incidents of overdose and abuse.
Actiq® (oral transmucosal fentanyl)	20-747	4 November 1998	None	<ol style="list-style-type: none"> 1. As per Duragesic except issues related to patch adhesion. 2. This product was associated with a high rate of dental caries although a new sugar-free formulation has largely mitigated this issue. 3. Because the product has the appearance of a lollipop, pediatric accidental ingestion has been observed although this was predicted by FDA and the risk management program. 4. There has been significant off-label use (~80% of the prescriptions have not been in cancer patients).

2.4 Important Issues With Pharmacologically Related Products

All opioids possess the potential for fatal respiratory depression. Opioids have a well established adverse event profile that includes sedation, nausea, vomiting, pruritis/urticaria, hypotension, and constipation. Abuse, tolerance, and physical dependence are other recognized risks with this class of drugs.

With regard to abuse and addiction, the most prominent opioid product of the late 20th and early 21st Century has been Oxycontin®, an extended-release formulation of oxycodone. Oxycontin® was approved in 1995. At the time of approval, the prevailing paradigm was that Oxycontin® would likely be less abused than the marketed immediate-release formulations of oxycodone because the extended-release pharmacokinetic profile prevented large swings in plasma oxycodone concentration, making for a less intense “rush.”

Oxycontin® became highly abused for several reasons. First, oxycodone is recognized as a comparatively euphorogenic opioid, therefore offering more reward for abusers compared to other opioid moieties. Second, being an extended-release product, Oxycontin® had more opioid per tablet. Third, many of the readily available oxycodone containing products (Percocet®, Percodan®) were combination products where the second ingredient limited the total amount of product that could be ingested or made the process of obtaining a concentrated amount of oxycodone difficult. Fourth, the single-agent immediate-release products had a high ratio of inactive excipients to oxycodone. Therefore, alternative methods of administration such as crushing the tablet and snorting required an abuser to snort large quantities of inactive ingredient. Last, Purdue Pharma, the manufacturer of Oxycontin® may have aggressively marketed Oxycontin® which resulted in a wider prescriber base than usual for a high potency opioid.

Abusers learned that the extended-release matrix in Oxycontin® could be defeated by crushing or chewing the tablet which produced a rapid, high peak plasma concentration when administered orally. Furthermore, pulverizing the tablets produced a powder with a relatively low excipient:opioid ratio and was “suitable” for abuse by snorting. Since there was no active second ingredient or large amount of excipient, it was easier to prepare Oxycontin® for injection. Abuse of Oxycontin®, via the oral, nasal, or intravenous routes became widespread and was associated with a substantial number of deaths.

Consequent to the experience with Oxycontin®, the Agency places significant resources into addressing abuse prior to approval and, in concert with the manufacturer, assists in formulating a Risk Minimization Action Plan (RiskMAP) to mitigate abuse once the drug is commercialized.

2.5 Presubmission Regulatory Activity

OVF has been developed under IND 65,447.

A pre-IND meeting was held with the original sponsor of the product (CIMA) on 1 November 2001. CIMA was advised of the following:

- At least one adequate and well-controlled study demonstrating efficacy in the proposed population would be required.
- The safety database should consist of at least 500 patients.
- The proposed strengths (200, 400, ~ μg) would not be sufficient. At a minimum, a dose roughly equivalent to the lowest dose of Actiq® would be required.
- Local tissue irritation would need to be monitored in clinical studies.

of Schedule II opioids to treat cancer pain" will have a significant impact on the RiskMAP

- This application will not be covered under Subpart H.
- The Division continues to support a deferral of pediatric study requirements.

On 10 August 2005, the Division of Medication Errors and Technical Support (DMETS) from the Office of Drug Safety opined that the proposed trade name _____ was unacceptable because _____, second proposed tradename _____ was also found unacceptable.

2.6 Other Relevant Background Information

No other background information is available because OVF is not approved in any other countries.

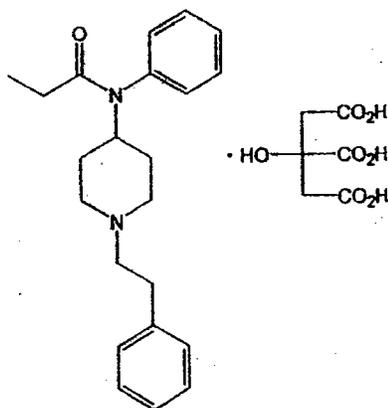
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Much on the information following is based on the applicant's NDA summary and the proposed product label.

3.1 CMC (and Product Microbiology, if Applicable)

Please see the Chemistry review for a detailed discussion of the CMC section (pending at the time of this review).

Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic molecule with an octanol-water partition coefficient at pH 7.4 of 816:1. It is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 and that of the citrate salt is 528.6. The compound has the following structural formula:



Clinical Review
Robert B. Shibuya, M.D.
NDA 21-947 (000)
TRADE NAME (Fentanyl buccal tablets)

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, magnesium stearate, and

REVIEWER COMMENTS: This is a 505(b)(2) application of fentanyl, which was first approved in 1968. The one chemistry issue with clinical significance pertains to the fact that OVF is formulated to effervesce and disintegrate against the buccal mucosa. To achieve this goal, the tablet

3.2 Animal Pharmacology/Toxicology

As a 505(b)(2) application, an abbreviated nonclinical development program was completed. The applicant's nonclinical program was limited to the mutagenic and clastogenic potential of three impurities in the active pharmaceutical ingredient.

REVIEWER'S COMMENT: According to the tabulated summary in the NDA, all of these studies were negative. Further details can be found in the Pharm/Tox review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data used in this review included the clinical study reports submitted by the Applicant and data from the labeling of related products.

4.2 Table of Clinical Studies

Table 2: Clinical Studies Conducted By Applicant

STUDY #	TYPE OF STUDY; OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	NUMBER OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
099-14	Safety and efficacy assessment in opioid-tolerant cancer patients with breakthrough pain	Randomized, placebo-controlled, crossover design	123 screened, 77 entered double-blind phase	Variable 68% of patients completed within 14 days	Complete; Full
C25608/3039/BP/US	Safety and efficacy assessment in opioid-tolerant cancer patients with breakthrough pain	Randomized, placebo-controlled, crossover design	71 screened, 47 entered double-blind phase	Variable 83% of patients completed within 14 days	Ongoing; Interim
099-15	Long-term safety assessment in opioid-tolerant cancer patients with breakthrough pain	Open-label, uncontrolled	208	Up to 12 months	Ongoing; Interim
C25608/3040/BP/US	Long-term safety assessment in opioid-tolerant <u>non-cancer</u> , chronic pain patients with breakthrough pain	Open-label, uncontrolled	406	Up to 12 months	Ongoing; Interim
099-16	Assessment of the effects of mucositis on the pharmacokinetics of OVF	Open-label, uncontrolled	20 planned (10 with mucositis, 10 without mucositis)	Single dose	Complete; Full
15 other single and multiple dose pharmacokinetic studies in 243 healthy volunteers					

4.3 Review Strategy

For this 505(b)(2) application, the applicant submitted a single adequate and well-controlled study, 099-014. The applicant is citing literature, the results of Study 099-14, and the Agency's previous findings of efficacy for the fentanyl moiety (injectable, transdermal, and oral transmucosal formulations) as substantial evidence of OVF's efficacy.

Review of the efficacy was conducted together with Dr. Yongman Kim, Division of Biometrics II. Dr. Kim reanalyzed and confirmed the applicant's analysis of the primary endpoint. A detailed description of all analyses and findings can be found in Dr. Kim's review.

The primary electronic datasets used for the efficacy analyses were those containing data for Study 099-14, specifically, *D_EPSR.XPT* and *D_ESPD.XPT*.

Data from all four Phase 3 trials were utilized in the integrated safety analysis. The safety review focused on adverse events, particularly deaths, serious adverse events, and morbidity related to the application site of the drug. The Integrated Summary of Safety (ISS) datasets that were used for the safety review are listed in Section 7.1

4.4 Data Quality and Integrity

Drs. _____ (Studies 14, 15, and 3039), _____ (Studies 14, 15, and 3039), _____ (Studies 14, 15, 3039, and 3040), and _____ (Study 14) were inspected. Minor protocol violations were noted such as one patient not having a hematology panel performed prior to enrollment, one patient received another investigational drug while on the open-label cancer study, etc. These protocol violations were not believed to affect the outcome of the studies inspected.

4.5 Compliance with Good Clinical Practices

Per the report from Division of Scientific Investigations, the studies appear to have been conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

Review of the Form FDA 3455 revealed that Dr. _____ received more than \$25,000 such as honoraria, grants, retainers, etc. each for studies _____. Therefore, the total special compensation to Dr. _____ is in excess of \$200,000. _____ of Dr. _____ site. Two other investigators, Drs. _____ also received >\$25,000 per study. The _____ site did not identify any significant issues and this reviewer feels that the special compensation did not affect the study results.

5 CLINICAL PHARMACOLOGY

Much of the material below is taken from the Dr. Chandra Chaurasia's Clinical Pharmacology review.

For this 505(b)(2) application, the applicant relied in part on data, including clinical pharmacology data, already available for Actiq® which relied, in turn, on data from Sublimaze®.

In addition, the applicant submitted six clinical pharmacology studies that contributed data to inform to the pharmacokinetics of OVF. These studies evaluated:

- Absolute and relative bioavailability
- Bioequivalence
- Dose proportionality
- Single and multiple dose pharmacokinetic characteristics

5.1 Pharmacokinetics

After transbuccal absorption of OVF, peak plasma levels of fentanyl are observed in 35-45 minutes in most individuals (range 20-181 minutes). The peak plasma concentrations and exposure (AUC) were observed to be approximately dose proportional over the proposed dosing range which supported the titration scheme. Compared to Actiq® (47%), the absolute bioavailability of OVF was demonstrated to be 65%. The half-life of OVF was related to the strength studied and varied from 2.63 hours for the 100 mcg tablet to 11.7 hours for the 800 mcg tablet. The reason for the wide variability in half-life is believed to be due to low plasma concentrations from administration of low strengths such that the plasma concentrations fall below the limit of detection more quickly than when high strengths are administered.

Dwell time (the interval between placing OVF in the mouth and complete dissolution) was measured for the clinical pharmacology studies. Dr. Chaurasia noted that the dwell time was highly variable, ranging from 4 to 77 minutes. Dr. Chaurasia analyzed whether this variability in dwell time had an effect on peak plasma concentration or overall exposure. He concluded that there was no apparent effect.

5.2 Pharmacodynamics

The applicant did not conduct any clinical pharmacology studies investigating the pharmacodynamics of fentanyl.

5.3 Exposure-Response Relationships

No tests informing to exposure-response were performed.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant seeks an indication of “the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain.” This indication is essentially identical to that of Actiq®, the approved formulation of oral transmucosal fentanyl citrate.

6.1.1 Methods

The applicant submitted Study 099-14 to support the efficacy of OVF as treatment of breakthrough pain in patients with cancer. The Division considered submission of a single adequate and well-controlled efficacy study, in the context of previous Agency findings for fentanyl, acceptable for an NDA submission.

6.1.2 General Discussion of Endpoints

The primary efficacy variable selected to support approval was pain intensity (PI) as estimated by a Numeric Pain Rating Scale (NPRS). The scale used the 0 (no pain) to 10 (worst pain you can imagine) range.

Pain intensity has become the preferred efficacy variable for the Division because it minimizes other psychosocial factors that a Patient Global Assessment of Study Medication includes and, unlike pain relief, a measure of pain intensity minimizes issues of recall.

Study 14 converted the raw PI scores into a Summed Pain Intensity Difference 30 (SPID₃₀) using the following formula.

$$SPID_{30} = (PI \text{ at } t = 0 \text{ minus } PI \text{ at } t = 15 \text{ minutes}) + (PI \text{ at } t = 0 \text{ minus } PI \text{ at } t = 30 \text{ minutes})$$

The theoretical maximum for the SPID₃₀ is 20 (a difference in PI of 10 for both timepoints). It is possible to generate negative numbers if the pain intensity increases for either or both recordings at 15 and 30 minutes.

The Division agreed to the NPRS, the use of a 0-10 range, and the calculated endpoint of a SPID₃₀ prior to the applicant initiating the trial.

6.1.3 Study Design

Table 3 enumerates the attributes of an adequate and well-controlled (AWC) study per 21 CFR 314.126 on the left column and how Study 099-14 met these attributes in the right column.

Table 3: Comparison Of Study 14 To Attributes of An Adequate And Well-Controlled Study

Attribute per 21 CFR 314.126	Study 099-14
Clear statement of objectives	The objectives were clear and appropriate.
Summary of the proposed methods of analysis	The protocol contained a sufficiently detailed statistical analysis section.
Valid comparison to a control	A placebo control was used.
Method of subject selection provides assurance that they have the disease being studied	The inclusion and exclusion criteria were appropriate for the proposed indication.
Method of assignment to treatment or control minimizes bias	The study used a crossover design such that assignment bias was not possible.

Adequate measures are taken to minimize the bias of subjects, observers, and analysts	Since patients become accustomed to taking the study drug in the titration phase, it can be argued that blinding is compromised during the double-blind phase. However, because of ethical issues with a parallel-group, placebo control in this study population, this design has become standard.
Methods of assessment of response are well identified and reliable.	The efficacy study outcomes were pain intensity, pain relief, and a global assessment of study medication. These are all commonly used in analgesic trials and the 11-point numerical rating scale used for the primary endpoint is preferred.
The analysis is adequate to assess the effects of the drug.	The appropriate statistical tests were applied to assess efficacy.

In the opinion of this reviewer, Study 14 provides adequate evidence of benefit.

1. The study entry criteria are defined precisely, are appropriate and are able to be extrapolated to the intended patient population.
2. This reviewer notes that the duration of the controlled portion of the study was short [10 episodes of breakthrough pain, which could have occurred within days (range was 3-71 days with 84/124 patients completing the double-blind phase within 14 days)]. However, in light of the Agency's extensive experience with the fentanyl moiety, it follows that the drug will remain efficacious for the expected lifespan of these patients with advanced malignancies although dose adjustment may be necessary.
3. Because of the method of use for this product (empirical dose finding via dose escalation), Phase 2 dose-finding studies were not required.

6.1.4 Efficacy Findings

The applicant's primary efficacy outcome was the Summed Pain Intensity Difference in the 30 minutes after dosing (SPID₃₀). This analysis was conducted for all patients meeting the Modified Intent To Treat (MITT) definition (patients who were dispensed double-blind medication AND took at least 1 active and 1 placebo dose AND have the predose and at least 1 post dose (either 15 or 30 minutes) pain intensity scores recorded by both episodes).

6.1.4.1 Protocol 099-14

(Refer to the Appendix for a detailed description of the study design, protocol amendments, statistical analyses, and study results).

Title: A Multicenter, Double-Blind, Placebo-Controlled Study of ORAVESCENT Fentanyl Citrate for the Treatment of Breakthrough Pain in Opioid-Tolerant Cancer Patients

Subject disposition:

One hundred twenty three patients were screened, all of whom received at least one dose of OVF. Of the 123 patients enrolled, 77 successfully completed the open-label dose titration phase and entered the double-blind, placebo-controlled phase. Sixty eight patients completed the double-blind phase.

Table 4, below, summarizes the reasons for dropout.

Table 4: Reasons For Patient Dropout And Numbers of Patients Who Dropped Out (Study 14)

Reason for dropout	Dropout during titration [N (%)]	Dropout during double-blind [N (%)]
Adverse event	12 (10)	3(2)
Lack of efficacy	20 (16)	0
Consent withdrawn	6 (5)	4 (3)
Protocol violation	0	0
Lost to follow up	1 (<1)	0
Other	7 (6)	2 (2)

Extent of exposure/Dosing information:

Because of the study design, the extent of exposure was small. During the titration phase, patients took between 1 and 10 doses of OVF and took 7 doses during the double-blind phase.

Table 5, below, summarizes the distribution of strengths used in the trial

Table 5: Final Titrated OVF Strength (Study 14) [from Table 13 of the Clinical Study Report for Study 14 (page 65)]

OVF Strength (µg)	Double Blind phase* [N (%)]
100	12 (16)
200	11 (14)
400	20 (26)
600	10 (13)
800	24 (31)

*Values from titration phase essentially identical

Demographics:

Due to the study design, there is no comparator group. Table 6, following, summarizes the demographic information for the patients (all enrolled patients – N = 123).

Table 6: Demographic Information For Patients In Study 14

Variable	Mean	SD	Range
Age (yrs)	58.0	12.6	27-87
Weight (kg)	74.7	18.5	40-147
Height (cm)	169.7	11.1	135-201
BMI (kg/m ²)	25.9	5.9	17-47
Sex	Male 67 (54%)	Female 56 (46%)	
Race	White 109 (89%)	Black 2 (2%)	Other 12 (10%)

The preponderance of the pain was located in the chest/abdomen/pelvis with a substantial proportion in the lower extremities and a smaller number in the upper extremities and head and neck. In the opinion of the investigator, the mechanism of pain was predominantly neuropathic in 19% of patients, predominantly nociceptive in 55%, and mixed in 26%.

Applicant's Efficacy Analysis:

Overview:

The applicant found that, with respect to the primary endpoint, episodes of breakthrough pain treated with OVF were associated with a statistically significant decrease in pain intensity compared to those episodes treated with placebo. Furthermore, for the 19 secondary endpoints, almost each one showed a statistically significant benefit for OVF with p-values ranging from < 0.0001 to 0.0029.

In summary, the applicant concluded that treatment with OVF is efficacious in the treatment of breakthrough pain in opioid-tolerant cancer patients.

Primary Efficacy Analysis: Summed Pain Intensity Difference over 30 minutes (SPID₃₀):

The sponsor applied the per protocol statistical analysis to the pain intensity data with the following results.

Table 7: Summary Statistics For The Primary Endpoint For Study 14 (SPID₃₀)

Statistic	OVF (N = 72)	Placebo (N = 72)	p-value
Mean	3.2	2.0	<0.0001
Standard Deviation	2.60	2.21	
Median	2.6	1.3	
Range	-1.0 to 12.7	-1.7 to 9.7	

Reviewer's Efficacy Analysis:

1. The applicant's statistical analysis was confirmed by Dr. Yongman Kim of the Division of Biometrics II. The p-value is highly significant and the primary endpoint, a measure of pain intensity, is acceptable for analgesic trials. In addition, Dr. Kim reanalyzed the

permutation test. He confirmed that the limitation in the number of randomization sequences did not affect the validity of the conclusion.

While the p-value was significant, this reviewer was concerned about the small size of the treatment effect. The difference in SPID₃₀ was 1.2 units. This represents the sum of the arithmetic difference between baseline and the pain intensity at 15 and 30 minutes on a 1-10 scale. Thus, the treatment effect for one comparison is only 0.6 units.

2. This reviewer applied another analysis to the data from Study 14 to assess the clinical relevance of the difference in pain intensity. The analysis is fully described in the Appendix.

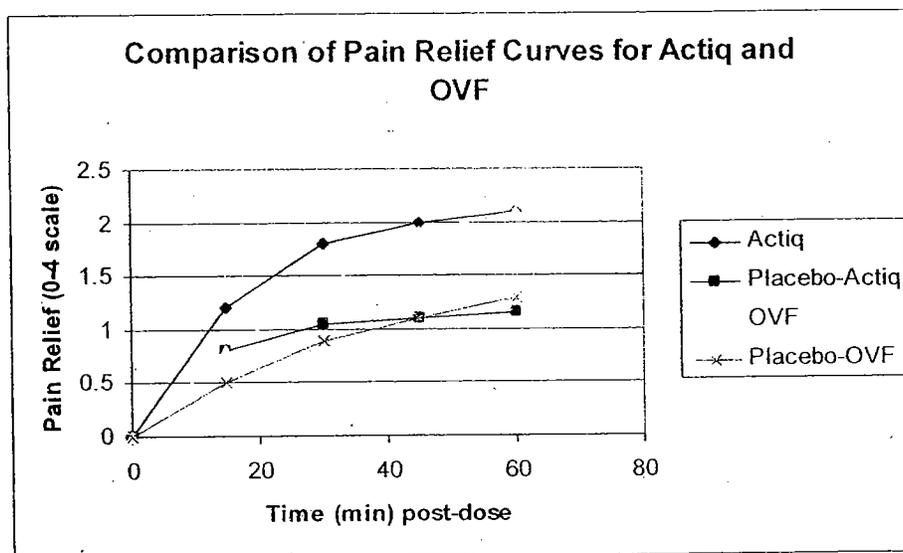
Briefly, Farrar et al¹ conducted a retrospective analysis of the data from the Actiq® trial in an attempt to better define what parameters of analgesia constitute a clinically significant effect. Data from the Actiq® trial were well suited to answer his question because of the design of the trial in the titration phase. Identical to Study 14, the Actiq® study titrated patients up from low strength product. The study captured whether rescue was necessary. Farrar reasoned that this was the gold standard for defining whether the analgesia achieved was clinically significant. If patients required rescue, the effect was inadequate. If patients did not require rescue, the analgesia was clinically significant.

Farrar used customarily calculated parameters from raw data [i.e. a summed pain intensity difference (SPID) from numerical pain intensity data]. Since the outcome (whether or not a patient required rescue) of each dose of Actiq® was known, Farrar was able to construct 2 x 2 tables analogous to those used for diagnostic tests from which he calculated sensitivity, specificity, and accuracy for an arbitrary cutoff. He changed the cutoff values for various calculated pain parameters, allowing him to evaluate the sensitivity, specificity, and accuracy rates for a given cutoff and parameter. On this basis, he was able to identify which parameters and cutoffs were most predictive of clinical significance. He concluded that six parameters were predictive. This reviewer subjected the data from Study 14 to Farrar's criteria. OVF met 5/6 of the criteria for clinical significance.

3. Complimentary to Farrar's reasoning, this reviewer notes that the protocol data includes a binary assessment of whether or not patients required conventional rescue analgesia following each dose of OVF or placebo during the double-blind phase. Again, this speaks to whether the treatment had a clinically significant effect. Rescue was used in 23% of the episodes treated with OVF versus 50% of episodes treated with placebo resulting in a relative risk ratio of 0.47 and a 95% confidence interval values of 0.37 to 0.60. Again, this supports that OVF had a clinically significant analgesic effect. Dr. Kim confirmed the applicant's analysis of this endpoint.
4. This reviewer compared the results of Study 14 to comparable results for the study that supported approval for Actiq®. The study designs were similar although the Actiq® study was conducted several years earlier. The Actiq® trial used pain relief (on a 0-4 scale) as the primary endpoint. Since these data were collected as secondary endpoints

for OVF, a comparison of the data can be made. Figure 3, below, is the comparison of these data.

Figure 3: Comparison of Mean Pain Relief Scores For Actiq® Pivotal Trial (Primary Efficacy Endpoint) and OVF Study 14 (Secondary Endpoint)



While comparison of inter-trial data is treacherous, the figure appears to show that the analgesic effect of Actiq® is observed sooner than that of OVF. Nonetheless, the separation between active and placebo curves appear similar.

6.1.5 Clinical Microbiology

This product is not an antimicrobial.

6.1.6 Efficacy Conclusions

In summary, when all of the data are weighed, this reviewer concludes that Study 14 supports a finding of efficacy for OVF for the intended indication.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In support of this New Drug Application, Cephalon is relying in part upon the Agency's previous finding of safety for the other approved fentanyl-containing drug products (Sublimaze®, Duragesic®, and Actiq®). The applicant has conducted four clinical trials to provide additional safety data specific to the OVF product. Data from these trials are summarized in the individual

study reports, the Summary of Clinical Safety, and SAS transport files for adverse events, laboratory data, and vital signs.

As previously stated, the assessment of safety for OVF is problematic. First, the patient population that provided a substantial portion of the safety database (patients with advanced cancer) were very ill, primarily due to the malignancy and its treatment but many had other comorbid conditions. Next, patients were on a wide variety of concomitant medications including treatments specific for their malignancy, other comorbid conditions, and around-the-clock opioids. Naturally, this makes distinguishing adverse events due to OVF very difficult. Third, due to the design of the controlled trial (a 10-period crossover conducted in as few as 5 days), for all intents and purposes, there is no control group for comparison. If the exact timing of the onset of the adverse event were known, it may be possible to attribute some adverse events to OVF. However, at least for the serious adverse events, this information is only available for 12% of the events.

7.1.1 Deaths

Fifty-three patients died while on a study in the OVF clinical development program. This reviewer evaluated the available information (narrative, case report form, data listings) for each death. None of the deaths could be definitively related to the use of OVF. Due to the large number of deaths, this review does not contain a summary of each case. Rather, pertinent facts are summarized in Tables A1-A3, located in the Appendix.

For this review, the deaths were divided into those due to progression of disease (e.g. tissue destruction due to direct extension of the tumor or a metastasis), those due to complications of the disease (e.g. sepsis secondary to leukopenia, secondary to chemotherapy), and those not related to the underlying malignancy (MI in a patient with adenocarcinoma of the colon). In many cases, placing the patient into one of these classes was not entirely straightforward due to the complex clinical course experienced at end of life. This reviewer used the entire clinical scenario in adjudicating whether the death was due to the underlying malignancy, due to a complication of the malignancy, or unrelated to the malignancy. Thirty-five deaths were felt to be due to progression of the malignancy, 15 due to complications of the malignancy, and 3 were not related to the underlying malignancy or chronic pain syndrome.

For the six cases where more explanation was appropriate, narratives were written, immediately following.

Individual Patient Death Summaries

Reviewer note: When reconciled with the case report forms, almost all of the calendar dates corresponded correctly with the "study day" reported in the submission. However, several discrepancies were found, generally when the screening and start of titration did not coincide. These discrepancies did not affect the conclusions. Therefore, for the sake of brevity, the sponsor's use of "study day" will be used.

Patient 47003 (Study 14) was a 62-year-old white man with an unknown cancer primary with hepatic and osseous metastases. His past medical history included peripheral vascular disease, abdominal pain, chemotherapy-induced leukopenia, iron deficiency anemia, neutropenia, and hypercalcemia (dating to February 2003 and said to be treated with pamidronate). The patient completed the titration phase and was entered the double-blind phase on Study Day 23. On Study Day 38, on which he took 400 µg of study drug, the patient was admitted to the hospital with hypercalcemia (Ca = 14.1 mg/dL-reference range 8.7-10.5 mg/dL). During the hospitalization, the patient had an episode of confusion. He was discharged on study day 40. On study day 45, he presented to his physician with confusion, constipation, and tremor. His serum calcium was 10.9 mg/dL (reference range 8.5-10.2 mg/dL). He was admitted to hospice the same day. The patient had another period of confusion the day after admission to hospice. He died 3 days later (study day 49).

REVIEWER COMMENT: This patient took one dose of double-blind study drug on study day 38. The same day he was admitted to the hospital with a serum calcium exceeding 14 mg/dL. This reviewer conducted a Medline search for hypercalcemia and fentanyl/opioids. No cases have been reported. Furthermore, this patient had an 18-month history of hypercalcemia. While it seems unlikely that the hypercalcemia was attributable to study drug, an association cannot be ruled out because of the temporal relationship of the drug administration and event.

Patient 57003 (Study 14) was a 68-year-old white man with prostate cancer metastatic to lung, liver, and bone. His past medical history included coronary artery disease, myocardial infarction, hypertension, diabetes, stomatitis, and anemia. The patient took 6 titration doses on study days 1, 2 (2 tablets on day 2), 9, 14, and 15. The patient reported some dizziness following the dose on study day 14. On study day 17, the patient complained of nausea, vomiting and dehydration. He was hospitalized for this and rapidly developed multiorgan failure. The admitting laboratory exams were significant for a potassium of 6.6 mmol/L, blood urea nitrogen 47 mcg/dL, creatinine 4.3 mcg/dL, AST 141 U/L, ALT 136 U/L, and a chest x-ray studded with numerous nodules consistent with metastatic disease. The patient declined therapy except comfort measures and died on study day 19. Given the advanced stage of the patient's cancer at the time OVF was first administered, this death cannot reasonably be attributed to OVF.

Patient 04002 (Study 15) was a 70-year-old woman with breast cancer and carcinomatous meningitis. She was rolled over into Study 15 from Study 14. Her pertinent medical history included mild encephalopathy. The patient experienced her first SAE on study day 1 (severe pain due to widespread bone mets) which resolved 8 days later. On study day 43, she experienced progression of her malignancy and moderate encephalopathy felt to be due to the spread of disease, not study drug. She continued to deteriorate, went to hospice care, and died 16 days later. Review of the available documentation leads this reviewer to conclude that OVF did not play a role in her death or SAEs.

Patient 59004 (Study 15) was a 55 year-old white man with prostate cancer. His past medical history included cirrhosis of the liver, rib and back pain, depression, neutropenia, anemia, thrombocytopenia, s/p colostomy, fatigue, nausea, and intermittent constipation. He was enrolled in Study 15 as a *de novo* patient and stabilized on a maintenance dose on study day 7.

This patient was enrolled on Study 15 for a total of 212 days. While on study, his clinical course was complicated by anemia, constipation, cancer pain, headache, fatigue, dizziness, nausea, asthenia, edema, depression, vomiting, dyspnea, jaundice, vertebral compression fracture, and mild tremor. He was on a wide variety of anti-neoplastic drugs, analgesics, and drugs to support his hematopoietic system and treat his depression over the time he was on study.

On study day 211 or 212, the patient experienced a decrease in level of consciousness for which he was hospitalized. The serum ammonia level was normal and he was diagnosed with altered mental status of unclear etiology. Apparently, narcotics were held to determine whether an overdose had occurred. The patient's mental status continued to deteriorate and he was pronounced dead on study day 214. The investigator opined that the change in mental status was due to progression of disease and not related to study drug. From the review of the available material, this reviewer agrees with the investigator's conclusion.

Patient 302003 (Study 15) was a 63-year-old white man with chronic myeloid leukemia. He had a long, complex medical history that included most significantly s/p heart transplant, renal and hepatic insufficiency, edema, hypertension, and depression. He was rolled over from Study 3039 at a maintenance dose of 100 mcg. Prior to enrollment in Study 15, he had experienced episodes of edema (facial, lower extremity, and scrotal). These were treated with varying degrees of success with furosemide. On study day 45 of Study 15, the patient presented to the Emergency Room with severe confusion, weakness, and lower extremity edema. His workup showed worsening renal failure and progression of the chronic myeloid leukemia. Since he was not a candidate for dialysis, his clinical status continued to decline and he was pronounced dead on hospital day 4.

Review of his study drug diary shows a total of 14 doses of study drug used for the 7 days prior to his final hospitalization and only 1 dose used the day prior to hospitalization (none used the day of hospitalization). There is no evidence to attribute the cause of death to study drug.

Patient 351003 (Study 15) was a 64-year-old white woman with small cell carcinoma of the lung. She had a complex medical history that included most significantly neurogenic bladder, nephrolithiasis, chronic urinary tract infection, confusion, grand mal, Jacksonian, and petit mal seizures, hyperammonemia, hypertension, pneumonia, obstructive sleep apnea, nausea, and dizziness. She was rolled over from Study 39 at a maintenance dose of 800 mcg. She was on multiple medications, mostly for symptomatic relief of pain, nausea, and psychiatric indications.

The patient experienced two serious adverse events, the second of which resulted in death. On study day 74, she was admitted to the hospital for mental status changes (excessive somnolence), decreased urine output, and poor PO intake. Study drug was held and the mental status changes eventually resolved. On study day 104, she became unresponsive at home. She was rehospitalized and found to be in hepatic failure secondary to metastases. She died two days later. Review of her study diary does not indicate any increase in her use of OVF (average 3 tablets/day) around the time of these events, nor any evidence of a relationship between OVF use and the mental status changes.

7.1.2 Other Serious Adverse Events

Seventy-eight patients (who did not die) experienced a total of 258 adverse events that met the definition of serious in the OVF clinical development program. This reviewer thoroughly reviewed the available information about each serious adverse event (SAE). Due to the large number of SAEs, this review does not contain a summary for each patient who experienced an SAE. Rather, pertinent facts are summarized in tabular form in the Appendix of this review.

The SAEs have been analyzed similarly to the deaths and have been categorized with respect to their etiology relative to the underlying disease. Unlike the deaths, a significant number of SAEs (44) were observed in 28 patients in Study 3040, in a patient population that did not have a malignancy. For the patients in Study 3040, causality was assessed with regard to the underlying morbidities, not to a malignancy. Nineteen patients experienced SAEs due to progression of the underlying disease, 20 due to complications of the underlying disease, and 39 experienced SAEs not related to the underlying disease.

Excepting four cases of overdose (see Section 7.1.4), 4 of the 78 patients experienced SAEs that, in this reviewer's opinion, were possibly related to OVF. These were one patient each with pneumonia/confusion, syncope, neurogenic bladder, and seizures. The SAEs are summarized in Tables A4-A6, located in the Appendix. Summaries where more detail is appropriate are included below.

In summary, the large majority of the SAEs could not be attributed to OVF. While some of the SAEs could be reasonably attributed to OVF, they represent events consistent with similar high potency opioids and, in the opinion of this reviewer, do not indicate that OVF is more dangerous than similar drugs in the class for the labeled opioid-tolerant patient population. Brief patient summaries and reviewer comments are provided for seven selected patients. Three SAEs that did not appear in the database have been included at the end of this section.

Individual Serious Adverse Event Summaries:

Patient 43005 (Study 15) is a 61-year-old white woman with breast cancer and metastases to the brain, lungs, bone, and right maxilla. Her past medical history includes congestive heart failure. She was a *de novo* patient who was stabilized on a maintenance dose of 600 mcg on study day 15. She experienced three adverse events while on study. On study day 18, she was hospitalized for tremors of the hands and legs and dyspnea. The tremors were felt to be a consequence of her brain metastases and the dyspnea due to a pleural effusion/atelectasis. On study day 100, she was hospitalized for a pulmonary embolus. On study day 116, she was hospitalized for confusion, dehydration, and leukocytosis. A review of her diary indicates that she had not taken any study drug for the 4 days prior to her confusional episode.

Patient 44005 (Study 15) is a 41-year old white woman with breast cancer metastatic to bone, brain, and liver. Her medical history included anemia, deep vein thrombosis, and left modified radical mastectomy. On study day 120, the patient developed pneumonia for which she was treated with Zosyn (piperacillin/tazobactam). She experienced anaphylaxis and a cardio-pulmonary arrest from which she was resuscitated and completely recovered by study day 146.

Later in the study (approximately study day 179), she experienced severe hypoxia due to a malignant pleural effusion. The effusion and resultant respiratory failure waxed and waned and she was withdrawn in study day 197 at the request of the investigator. In the opinion of this reviewer, the anaphylaxis, malignant effusion, and respiratory failure were not related to OVF.

Patient 304005 (Study 15) is a 56-year-old white woman with multiple myeloma s/p peripheral stem cell transplant and a past medical history significant for hypertension, obesity, hepatitis, and anxiety. She was rolled over from Study 39 on a maintenance dose of 800 mcg. On study day 69 she began to experience syncope and near syncope. Apparently, she was hospitalized on study day 99 after two episodes of syncope in her home. During this period of time, the patient was having her antihypertensive medications adjusted for her labile hypertension. The cardiac workup was negative except first degree heart block on ECG. The investigator opined that the syncopal episodes were not related to study drug.

REVIEWER COMMENT: Review of this patient's diary shows that she used 3-4 tablets/day for the month prior to the first episodes of syncope (on study day 69). Her use of study drug increased to 5, 4, 8, 6, 6, and 5 tablets per day from on study days 70-75 respectively. Unfortunately, following this, the patient discontinued using her diary although she says she continued taking study drug. She remains on the study. It appears likely that episodic hypotension is responsible for the syncope although, given the increased use of OVF during the period that she became symptomatic, it is possible that OVF played a role in this patient's serious adverse events.

Patient 025003 (Study 3040) is a 54-year-old woman with chronic low back pain. Her medical history includes, among other problems, depression (x 11 years), multiple sclerosis (x 11 years), s/p fractured vertebrae (motor vehicle accident, 3 years prior to enrollment), and hypothyroidism. She reached a successful dose of 200 µg on study day 4. On study day 130, she attempted suicide (polydrug overdose, including opioids and OVF). The investigator learned about the SAE when his office attempted to contact the patient to learn why she had missed a visit. The patient said that she would be hospitalized for the foreseeable future and wished to discontinue the study since she could not attend the visits. The investigator opined that the exacerbation of depression/suicide attempt was not associated with OVF.

REVIEWER COMMENT: According to the drug administration records, this patient's last dose of OVF was 7 days prior to her suicide attempt. According to other records, OVF was used during in her suicide attempt. As a class, opioids are not are not known to cause depression. Again, this patient was on chronic opioids (oxycodone, extended-release, 180 mg/day). She also had an 11-year history of depression. For all of these reasons, this reviewer cannot attribute the suicide attempt to OVF. This reviewer notes however, that OVF was used in the attempt. While unfortunate, the use of opioids for intentional overdose has, is, and will continue to occur. There did not appear to be anything specific to OVF that implies excess risk in this formulation of the product.

Patient 025015 (Study 3040) is a 47 year-old white woman with pain due to chronic headache. Her past medical history includes severe gastroparesis (which was diagnosed as celiac sprue during the hospitalization reported as an SAE), and narcolepsy. She has had multiple surgeries

for her GI complaints including a truncal vagotomy, antrectomy, Billroth II with enterostomy, and a Roux-en-Y and vagotomy. On study day 79, the patient was at home when she fell to the floor. She had just returned to her home following an appointment two days earlier with a gastroenterologist at the _____ The patient reported essentially no PO intake for the two days prior to the syncopal episode/fall. The patient was treated with crystalloid with improvement in her general condition, mental status, and appetite. She was discharged on a gluten free diet the day after admission. Her attending physician opined that the fall and delirium were due to acute dehydration. This reviewer agrees with the opinion of the attending physician.

Patient 031016 (Study 3040) is a 43-year-old white woman with chronic low back pain. Her past medical history is significant for pulmonary hypertension due to obesity-hypoventilation syndrome, hypothyroidism, mesenteric vasculitis, ischemic colitis, and anasarca. On study day 29, the patient was hospitalized for an acute exacerbation of pulmonary hypertension, anasarca, and a syncopal episode. She was treated with diuresis and BiPAP with gradual improvement in her clinical status. In this reviewer's opinion, the episode was due to the patient's underlying comorbidities, not OVF.

Patient 034037 (Study 3040) is a 20 year old white man with chronic pain due to nephrolithiasis. His medications at the time of the SAE included meperidine, carisoprodol, diazepam, hydrocodone/APAP, oral transmucosal fentanyl, oxycodone, methamphetamine, and another formulation of fentanyl (presumably transdermal). Apparently, he experienced a witnessed tonic-clonic seizure of approximately 10 minutes duration. Questioning by the Emergency Department staff revealed that he had been having episodes of vomiting and acting "like he is not really with it." A CT of the head was negative. He received crystalloid and was started on valproic acid.

REVIEWER COMMENT: This patient experienced a seizure while on a number of opioids, in particular meperidine. From what this reviewer can discern, the meperidine was administered chronically, which, due to the accumulation of normeperidine, lowers the seizure threshold. In this reviewer's opinion, the seizure was more likely due to the chronic administration of meperidine, not to the OVF.

The following three SAEs were not submitted in this NDA (they occurred after data lock) but were reported to IND 65,447, serials 063, 064, and 083.

Patient 3040-003-003021 (Study 3040) is a 47 year old woman with a history of chronic low back pain, depression, insomnia, and a previous suicide attempt. Her medications at the time of study enrollment included hydrocodone/acetaminophen, cyclobenzaprine, temazepam, bupropion, and duloxetine. She was titrated to a maintenance dose of 800 µg. Two days after reaching her maintenance dose, the patient was found unconscious and cyanotic. She was intubated and ventilated. EMTs reported a significant quantity of bourbon and whiskey in the vicinity of the patient. She was admitted and diagnosed with a poly-drug overdose. Her toxicology screen was additionally positive for barbiturates (not prescribed). After recovering,

she admitted self-administration of six 800 µg tablets over an eleven-hour period although she said that she was not suicidal. The investigator opined that the SAE was likely due to OVF.

REVIEWER COMMENT: Upon receipt of this 15-day expedited report, the Division contacted the applicant by telephone. The Division was also concerned because the SAE report indicated that the patient was continued on study after this episode of intoxication. However, during the teleconference with the applicant, the Division learned that the patient did not report the event until her next visit to the investigator where she was discontinued from the study. While it is likely that OVF contributed to the serious and severe respiratory depression, this is an unavoidable consequence of the irresponsible use of the drug that will occur with a small percentage of patients.

Patient 3042-503-503003 (Study 3042) is a 60-year old man with a history of chronic low back pain with breakthrough pain. Other pertinent medical history includes depression, anxiety, and bipolar disorder. His medical regimen at study entry included: divalproex sodium, sertraline, ropinarole, baclofen, lorazepam, oxycodone, tiagabine, and etodolac. The patient was enrolled in study C25608/3042/BP/US, entitled "A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oravescent Fentanyl Citrate for the Management of Breakthrough Pain in Opioid-Tolerant patients with Chronic Low Back Pain."

The patient was in the open-label titration phase and had escalated his dose to 4 x 100 µg tablets/episode at the direction of the investigator. The patient was left unattended for several minutes. When his wife returned, he was unresponsive. EMS was summoned and CPR was initiated. The patient revived upon receiving supplemental oxygen. The patient was admitted to the hospital for observation.

REVIEWER COMMENT: The applicant was contacted regarding this SAE upon receipt of the 15-day expedited report. The applicant said they had learned that, instead of taking 4 x 100 µg tablets as directed, he took 4 x 600 µg tablets, resulting in the overdose. The applicant stated that they were unaware of any other dose mix-ups. The applicant stated that all five to-be-marketed strengths (100, 200, 400, 600, & 800 µg) are dispensed at the titration visit. This reviewer includes this SAE report in the review for NDA 21-947 because, in this reviewer's opinion, the practice of dispensing all 5 strengths cannot continue once the well-controlled environment of a clinical trial is breached and the drug is marketed widely.

Patient C25608/3040/017 (Study 3040) is a 54 year-old man with a history of chronic low back breakthrough pain. He has a history of disc herniation, status post laminectomy and spinal fusion, muscle spasms, radiculopathy, and bipolar disorder. The patient was managed with immediate-release oxycodone, oxycodone/acetaminophen, and propoxyphene/acetaminophen for his pain. He experienced two SAEs. On study day 76, he was found unresponsive and in respiratory distress. He was transported to the emergency department and treated with naloxone with resolution of his symptoms. After this incident, the patient was discontinued from the study.

Two days later, the patient was seen in the emergency room again, this time with mental status changes and “violent body spasms.” He told the medical staff that he had continued his opioids although a urine drug screen was negative. He was treated with lorazepam, haloperidol, and transdermal fentanyl. A neurologic workup consisting of a head CT and EEG was negative and the symptoms resolved. His discharge diagnosis was narcotic withdrawal syndrome.

REVIEWER COMMENTS: The MedWatch Form indicates that this patient self-administered five 800 mcg tablets of OVF, his usual around-the-clock opioid (immediate-release oxycodone dosed every 6 hours), plus additional oxycodone/acetaminophen the day of his intoxication. It is not clear why he was prescribed additional oxycodone/acetaminophen since he should have been using OVF for rescue. However, the investigator appropriately discontinued him from the study. This case provides more support for a strict risk minimization action plan to ensure that the correct patient population is prescribed OVF.

The second SAE could have represented drug withdrawal. However, many of the most prominent features of withdrawal such as nausea, vomiting, diaphoresis, and pain were not described.

7.1.3 Dropouts and Other Significant Adverse Events

Sixty-four patients dropped out for adverse events that did not meet the definition of serious. This reviewer assessed the available information to adjudicate whether the incidents that led to discontinuation were definitely or probably due to OVF. Forty-six of the 64 patients were felt to have discontinued (definitely or probably) due to OVF. For these patients, the AEs leading to discontinuation are tabulated below. NB 1) Most patients reported more than one adverse event that led to discontinuation and 2) Symptoms only mentioned once are not included in Table 8.

Table 8: Patients Who Dropped Out Prematurely Due To Adverse Events

Adverse Event	Number of times AE was listed as leading to dropout
Nausea	23
Vomiting	14
Application site abnormalities*	12
Dizziness	11
Drowsiness/sedation	7
Headache	5
Visual symptoms (blurry)	5
Pain (other than oral cavity pain)	4
Hyperhidrosis	4
Anxiety	3
Tremor	2

*Discussed in further detail following

Further information regarding these dropouts is available Table A7 in the appendix.

Application Site Abnormalities:

In the initial review of the adverse event safety database, this reviewer was struck by complaints related to the application site (between the cheek and a maxillary molar). The verbatim terms spanned a wide spectrum and included:

1. Application site irritation
2. Application site ulcer
3. Application site pain
4. Application site nodule
5. Application site vesicles
6. Application site bleeding
7. Application site erythema
8. Application site discomfort
9. Application site anesthesia
10. Application site swelling
11. Application site (o)edema
12. Application site reaction
13. Application site paresthesia

A total of 71 patients reported adverse events pertaining to the application site and 12 patients withdrew from the study prematurely due to application site issues. This reviewer also noticed that, while the large majority of the adverse events were noted to resolve, two patients had the outcome coded as "resolved with residual effect." This reviewer further noted that a substantial proportion ($47/71 = 66\%$) occurred in Study 3040, the non-cancer study where the oral mucosa would be expected to be normal.

To address these issues, the applicant was asked to further analyze the application site complaints. Pertinent points from the applicant's discussion follow.

1. The lesions tend to develop after short-term exposure (69% of patients developed the complaint during titration).
2. The most common signs and symptoms were pain (30 cases), ulcer (20 cases), and irritation (18 cases).
3. The percentage of patients describing the event as mild, moderate, and severe was 76%, 21%, and 3%, respectively, and none of the events met the definition of serious.
4. It appears likely that the lesions are self-limited although a substantial percentage (25%) persisted for 8-30 days after the initial complaint. Eighty-seven percent of the events were reported as resolved without sequelae. Ten percent of events were continuing at the time of data lock. Three percent (see #5 below) were coded as resolved with residual effect.
5. For the two patients who were coded in the SAS transport file as "resolved with residual effect," one was lost to follow up and the symptoms of the other had resolved but had been erroneously coded.

REVIEWER COMMENT: The proposed label

. Mucosal ulceration in a debilitated patient could lead to medically significant superinfection. OVF resulted in application site ulcers in 10 patients in the cancer trials (3.3%). In the opinion of this reviewer, a discussion of the application site lesions should be placed in the Precautions section, advising prescribers to monitor the oral cavity and warn patients. This should also be addressed in the Medication Guide, warning patients to seek medical attention if they develop complaints at the application site.

7.1.3.1 Overall profile of dropouts

A substantial number of patients (57) dropped out of the OVF trials and were coded as "withdrawal of consent." The sponsor was asked to provide additional information elaborating the specific reason for the withdrawal of consent.

The reasons for withdrawing consent are summarized below.

Table 9: Reasons For Discontinuation Which Were Coded As "Consent Withdrawn"

Reason	Number of patients
Family/caretaker issues	6
No or insufficient pain	7
Problems learning to use Palm Pilot	5
Coming for visits too much trouble, cannot fulfill obligations, got tired of study, got tired of filling out diary	20
Fearful of addiction	1
Moved or changed doctor	4
Lack of efficacy	6
Prefers old rescue medication	2
Cannot keep tablets in mouth, tablets don't dissolve quickly enough	3
Unknown	3

REVIEWER COMMENT: Review of the data submitted does not raise concern that dropouts due to adverse events were coded as "consent withdrawn."

7.1.3.2 Adverse events associated with dropouts

Please see section 7.1.1

7.1.3.3 Other significant adverse events

Mucositis is a fairly common ailment in the proposed patient population. It has been estimated that 40% of all patients newly diagnosed with cancer can be expected to experience oral mucositis related to the natural history of the disease or as a complication of treatment.

In discussions with the Division during the clinical development phase, the Division encouraged the applicant to evaluate the effect of mucositis on the pharmacokinetic characteristics and safety of the drug.

Applicant's Pharmacokinetic Evaluation of Mucositis Effects:

Pursuant to the Division's requests, the applicant conducted Study 099-16. This was a single-dose (200 µg) open-label study in patients with (grade 1-3 clinical examination findings and grade 1-2 functional/symptomatic findings-Common Terminology Criteria for Adverse Events) and without mucositis. In a submission dated 29 March 2006, the applicant provided the study report.

Nineteen patients were screened and 16 patients (8 with and 8 without mucositis) completed the study. The severity of the mucositis is summarized below.

Table 10: Grades Of Mucositis Enrolled In Study 16

Scale	Grade	Number of patients
Clinical	1	8
Clinical	2	0
Clinical	3	0
Functional	1	7
Functional	2	1
Functional	3	0

Pharmacokinetic findings: Briefly, within biological and experimental variability, the only difference between the groups was the AUC_{0-8} where that mean AUC was 25% higher in the patients with mucositis. Pertinent data (means) are summarized in the table following. With the exception of t_{max} , where the values represent the range, values following the means represent the standard deviation.

Table 11: Key Pharmacokinetic Parameters In Patients With And Without Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0-t_{max}}$ (ng-hr/mL)	AUC_{0-8} (ng-hr/mL)
Mucositis	1.25±0.78	25.0 (15-45)	0.21±0.16	2.33±0.93
No mucositis	1.24±0.77	22.5 (10-121)	0.25±0.24	1.86±0.86

With regard to clinical safety in Study 16, one patient with mucositis developed dizziness. In the non-mucositis cohort, one patient experienced anemia, one reported back pain and nausea, and one reported dizziness. No treatment-related abnormal vital signs were documented. None of the patients with normal oral cavity exams prior to dosing developed abnormalities nor did the grade of mucositis change in the patients who had mucositis prior to dosing.

Given the results of Study 16 and the fact that the proposed patient population for OVF is opioid-tolerant, in this reviewer's opinion, the findings from Study 16 do not raise significant safety issues for patients with mucositis. This reviewer notes that the severity of the mucositis in the study was mild.

Clinical Evaluation of Mucositis Effects:

In May of 2005, the applicant amended the ongoing cancer studies (Studies 15 and 3039) to include patients with xerostomia and mucositis/stomatitis of Grade 2 or higher to evaluate the effects of more severe mucositis on the safety of the drug (the previous versions of the protocol excluded patients with xerostomia and more severe mucositis).

In reviewing the SAS transport file containing information about the oral cavity examinations (*D_OE.XPT*), only one patient (C25608-09914/47/47008/DB) was coded as having "mucositis" at baseline although it was Grade 1. However, 73 other patients had abnormalities noted on their oral cavity exams at screening and over the course of their participation in the trial. Review of the line listings for these patients revealed that most of these oral cavity abnormalities were anatomic (status post radical neck dissection) or not likely to describe mucositis (dental caries, gingivitis).

Further review of the line listings allowed this reviewer to identify a total of 11 patients in the cancer studies who developed abnormal oral cavity examinations that might have represented mucositis (erythema, ulceration, pseudomembrane, friability, necrosis). The following table shows how many patients in each study were likely to have experienced mucositis at any time.

Table 12: Patients With Possible Mucositis Identified In Oral Exam Database

Study #	Number of patients presumed to have mucositis at any time
15	6
3039	5

This reviewer reviewed the line listings for these patients from the adverse event SAS transport file (*D_AE.XPT*). One of these 11 patients (9%) reported no adverse events (compared to 27% of the total safety population who did not report an adverse event).

- 4/11 patients reported adverse events consistent with opioids: constipation, nausea, and dizziness. None of the opioid-related adverse events were serious. All of the adverse events were mild in severity with the exception of two patients who complained of moderate dizziness.
- 4/11 patients experienced a total of 7 serious adverse events. In each case, the serious adverse event was direct progression or a complication of the underlying malignancy.

REVIEWER COMMENTS:

The pharmacokinetic data, show a modest increase in overall fentanyl exposure in patients with mild stomatitis compared to patients without stomatitis. In these opioid-

tolerant patients, these increases are unlikely to pose a significant safety hazard. A review of abnormalities from the oral examination database showed 11 patients with oral abnormalities that may have represented mucositis/stomatitis. The study did not collect data that graded the severity of these abnormalities. However, based upon the verbatim description, the lesions would probably represent Grade 1 on the NCI CTCAE scale. Given that, as described in the analysis conducted by this reviewer, there did not appear to be any excess toxicity that was serious or medically significant in these 11 patients.

In the opinion of this reviewer, the safety of OVF in patients with mucositis/stomatitis is supported for patients with Grade 1 stomatitis, based predominantly on Study 16.

7.1.4 Other Search Strategies

In assessing the safety of fentanyl and other related products and in reviewing the adverse event database in its totality, this reviewer identified four areas for special consideration, following.

1. Application site complaints-addressed in section 7.1.3
2. Intoxication/respiratory depression/apnea- At the time this review was written, there were five cases of intoxication/poisoning/respiratory depression involving the use of OVF.
 - a. Two patients attempted suicide while on an OVF study. One patient (#C25608-09915/88/8801) did not use OVF in the attempt, the other (#C25608/3040/BP/US/025/025003) had a history of depression and ingested a mixture of medications, including OVF. Neither patient completed their suicide.
 - b. One patient (#C25608/3040/003/003021) was found unconscious and cyanotic. She was diagnosed with a multiple drug overdose (alcohol, opioids, barbiturates (for which she did not have a prescription), and benzodiazepines). She denied suicidal ideation and admitted to using six OVF units in the previous 11 hours prior to being found.
 - c. One patient (#C25608/3042-503-503003) became confused during the titration phase and self-administered 4 x 600 mcg tablets, instead of 4 x 100 mcg as he had been instructed.
 - d. One patient (#C25608/3040/017) was found unresponsive and in respiratory distress as described in the Serious Adverse Events narratives. He self-administered a combination of immediate-release oxycodone, oxycodone/acetaminophen, and OVF, was found unresponsive, and required naloxone to reverse his symptoms.
 - e. On 17 April 2006, the Division was notified via FAX that the husband of a patient in Study 3040 was found dead, presumably due to OVF intoxication. OVF was suspected because the patient reported that 12-18 800 mcg tablets were missing from her study supplies. An autopsy is pending at the time this review was written.
3. Aspiration/pneumonia - One adverse event that is plausible because of the pharmacodynamics of fentanyl (nausea, vomiting, and sedation) and the pharmacokinetic profile of this product is aspiration, pneumonia, or aspiration pneumonia. This reviewer searched the complete safety database for all cases coded as "pneumonia" or "aspiration." There were a total of 18 cases. Ten of the cases meeting the definition of serious

occurred in the cancer population. Sixteen events occurred in cancer patients, two in non-cancer patients. The incidence then, is 5% in the cancer population (which is pertinent for this review). This incidence is not surprising given the rapidly declining clinical and functional status of patients with advanced malignancies. This rate approximates the rate of 8% found in patients with advanced hematological malignancies by Germania et al.²

4. Withdrawal-At the time of the writing of this review, there were two cases of possible withdrawal. One patient (#C25608/3040/013/013017) was described in the Serious Adverse Event narratives. In the opinion of this reviewer, it is not clear whether his symptoms were attributable to opioid withdrawal. The other patient (#C25608/09915/065/065001) is a 43 year-old woman with metastatic breast cancer and multiple other medical problems. Her opioid regimen included transdermal fentanyl and OVF. Her OVF requirements were high (approximately 10 tablets of 800 mcg per day) without complete alleviation of her breakthrough pain. She stated that she was worried that she was becoming addicted to OVF to the investigator. She was discontinued and instructed to increase the dose of the transdermal fentanyl. Soon after being discontinued, she experienced shaking, achiness, agitation, and nausea. She was hospitalized and treated with clonidine, lorazepam, and transdermal fentanyl with resolution of her symptoms.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All spontaneously reported, elicited, and observed AEs were documented on the adverse event reporting form. Data collection for AEs commenced after screening and continued until the time of data lock (30 October 2005). However, data used to generate the tables and prose in the Summary of Safety for the 120-day Update used a cutoff of 30 days following the end of treatment which resulted in minor discrepancies between the SAS transport file (*D_AE.xpt*) and the tables and prose in the report.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using MedDRA version 7.1. The appropriateness of the applicant's coding was evaluated by comparing the preferred terms to the verbatim terms recorded by investigators on the adverse event reporting form. In the opinion of this reviewer, the coding was reasonably accurate.

7.1.5.3 Incidence of common adverse events

Cephalon used all available data for the patients with cancer to construct Tables 4 and 5 that were used in the proposed package insert. Table 4 is a summary of the adverse events that occurred during titration at a rate $\geq 5\%$. Table 5 is a summary of adverse events that occurred during long term treatment at a rate $\geq 5\%$. As was done for Actiq, the applicant proposes to report the incidence of adverse events without correction for concomitant drug use, duration of

OVF therapy, or cancer-related symptoms. Because of the limitations in assessing the safety database discussed earlier in this review, this reviewer agrees with this approach.

7.1.5.4 Common adverse event tables

Using the SAS transport files provided in the 7 April 2006 submission, this reviewer verified the counts for adverse events occurring at a rate $\geq 5\%$ during titration for the cancer trials (Table 4 in the package insert) by maximum dose (including 4-month safety data). Counts from this reviewer's analysis are in the table below.

Table 13: Reviewer's Counts of Selected Adverse Events During Titration Phase Of Cancer Trials

System Organ Class MeDRA preferred term	100 mcg	200 mcg	400 mcg	600 mcg	800 mcg	Total
Nausea	4	5	10	13	—	50)*
Vomiting	0	2	2	7	3	14
Fatigue	3	1	9	1	5	19
Dizziness	5	2	12	18	21	58
Headache	1	3	4	8	10	26
Somnolence	2	2	6	7	3	20

*Applicant's table includes two patients who reported nausea but were lacking titration dose information.

Using the SAS transport files provided in the 7 April 2006 submission, this reviewer verified the counts for selected adverse events occurring at a rate $\geq 5\%$ during long-term therapy (including 4-month safety data). Counts from this reviewer's analysis are in the table following.

Table 14: Reviewer's Counts of Selected Adverse Events During Maintenance Phase of Cancer Trials

System Organ Class MeDRA preferred term	100 mcg	200 mcg	400 mcg	600 mcg	800 mcg	Total
Anemia	6	4	4	5	7	26
Neutropenia	0	2	1	4	4	11
Constipation	5	4	5	4	6	24
Diarrhea	3	0	4	3	5	15
Edema peripheral	6	5	4	5	3	23
Pneumonia	1	5	1	1	4	12
Anorexia	1	2	4	3	6	16
Hypokalemia	0	2	0	1	8	11
Headache	2	1	4	5	8	20
Depression	2	1	4	3	5	15
Confusional state	3	1	2	3	5	14
Dyspnea	1	6	0	7	4	18
Cough	1	1	2	4	5	13

Discrepancies between the SAS transport files and the applicant's table appear in italics. This reviewer's count is placed to the left and the applicant's proposed number in the table is in parentheses. In the opinion of this reviewer, the differences are insignificant and the applicant's proposed tables are acceptable.

7.1.5.5 Identifying common and drug-related adverse events

See Sections 7.1.2.3 and 7.1.2.4.

7.1.5.6 Additional analyses and explorations

See Section 7.1.4.

7.1.6 Less Common Adverse Events

During the review of the integrated safety database, no unusual adverse events were noted.

7.1.7 Laboratory Findings

In the clinical program, the laboratory evaluation of safety was conducted using standard hematology and chemistry tests. As explained further below, the analysis of the laboratory data is confounded by: