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RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 13, 2011
From	Sharon Hertz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202-788
Supplement#	
Applicant	Insys Therapeutics, Inc.
Date of Submission	March 14, 2011
PDUFA Goal Date	January 4, 2012
Proprietary Name / Established (USAN) names	Subsys/ Fentanyl Sublingual Spray
Dosage forms / Strength	Single dose sublingual spray/ 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
Proposed Indication(s)	Management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain
Recommended:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Luke Yip, M.D.
Statistical Review	Yan Zhou, Ph.D., Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D., Dan Mellon, Ph.D.
CMC Review	Julia Pinto, Ph.D., Prasad Peri, Ph.D.
Biopharmaceutics Review	N/A
Product Quality Microbiology Review	Bryan Riley, Ph.D.
Clinical Pharmacology Review	Wei Qiu, Ph.D., Yun Xu, Ph.D.
CDRH/ODE/DAGID/GHDB	LCDR Alan Stevens, Jacqueline Ryan, M.D.
DSI	John Lee, M.D., Susan Thompson, M.D.
OSE/DMEPA	Anne Tobenkin, Pharm.D.
OPDP/DDTCP	Sharon Mills, BSN, RN, L. Shenee' Toombs, Barbara Fuller, RN, MSN, LaShawn Griffiths, MSHS-PH, BSN, RN
CSS Review	Chad Reissig, Ph.D., Silvia Calderon, Ph.D.
Project Management	Kathleen Davies, Sara Stradley

1. Introduction

This is a 505(b)(2) application for Subsys, a sublingual, transmucosal, immediate-release formulation of fentanyl packaged in a single-dose spray device. During development, the product was referred to as fentanyl sublingual spray and is referred to as FSS throughout this review. The listed drug referenced by this application is Actiq (NDA 20-747). For this reformulation of fentanyl, one efficacy study, several pharmacokinetic studies and two open-label safety studies were submitted in support of this application.

2. Background

This application represents the sixth NDA for a transmucosal immediate-release fentanyl (TIRF) product indicated for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due to the similarity in appearance to a lollipop. A RiskMAP was created to attempt to manage the risks associated with this product. In addition to providing some methods to try and minimize the risk for accidental pediatric exposure, other goals described in the RiskMAP included preventing use in opioid non-tolerant patients and other unsafe off-label use. Fentora (NDA 21-947) was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. Fentora was approved with a RiskMAP comparable to Actiq.

Onsolis (NDA 22-266), Abstral (NDA 22-510) and Lazanda (NDA 22-569) followed Actiq and Fentora. Onsolis is formulated as a bioerodible membrane that adheres to the buccal mucosa. Abstral is a sublingual tablet formulation. Lazanda is formulated as a nasal spray. These three products were approved with risk evaluation and mitigation strategies (REMS). The reason for the switch to a REMS is described below.

The indication for this group of products, the management of breakthrough cancer pain in adult patients who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain is narrow for two reasons. First, the population identified has a specific need for a treatment to address cancer-associated breakthrough pain, which is characterized by a quick onset, often high severity, and relatively short duration. These formulations of fentanyl are designed to have a relatively rapid rise to C_{max} and a relative short duration of effect. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patients to be opioid-tolerant, a physiological state in which patients are more tolerant to the CNS depression and respiratory depression associated with opioids.

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

Postmarketing trends have also shown an increasing number of nonopioid-tolerant patients being prescribed TIRFs and reports of deaths in opioid nontolerant patients. The TIRFs are not bioequivalent with one another, and in spite of warnings in the labeling, have been inappropriately substituted in the pharmacy and by prescribers. As a result, the Agency determined the risks associated with these products would be better addressed through a REMS than the original risk management programs. Abstral, Onsolis and Lazanda were approved with REMS. To reduce the burden to the healthcare community, a TIRF class REMS has been developed. All five of the previously approved products are being rolled into this class REMS including Actiq and Fentora which have yet to stand up their own individual REMS. Subsys will be a part of this class REMS as well.

3. CMC/Device

The following is from Dr. Pinto's review:

The drug substance, fentanyl base, is a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors. The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl base is provided in DMF (b) (4). The API is made by (b) (4) at their (b) (4) facility which is recommended as adequate by OC (report attached in the appendix). The API will be stored and shipped in (b) (4) and has a retest period of (b) (4). The DMF has been reviewed and found to be adequate (P. Maturu, Rev #4 June 2009 and J. Pinto, Rev #5, Oct 2011).

The drug product is formulated as a sublingual, single-dose spray in concentrations of 1 mg/ml, 2 mg/ml, 4 mg/ml, 6 mg/ml and 8 mg/ml, with a total fill per vial of (b) (4). The dose is (b) (4). The formulation consists of the active substance, in dehydrated alcohol, propylene glycol, water, xylitol and menthol. The pump consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder. (b) (4)

Three packaging configurations are planned containing 6, 14, or 28 devices in a carton. Each carton includes a disposal system to accommodate both used and unused devices. The disposal system consists of a plastic container (b) (4) and a sealable pouch. The (b) (4) container is used for the collection and disposal of fentanyl solution from unused FSS units; the pouch is designed for the disposal of used/discharged FSS units. The DP is made by DPT at their Lakewood, NJ facility which was inspected has been recommended as adequate.

Dr. Pinto reviewed extraction studies of the (b) (4) bottle, holding 28 units of the maximum strength drug product. The studies were intended to evaluate the amount of recoverable fentanyl. The results show that there is some recovery of fentanyl with extraction using acetone, alcohols (dehydrated, isopropanol), ethyl acetate and 6N HCl. The most fentanyl recovered was (b) (4) using dehydrated ethanol which is equivalent to about 1.3%. Heat, shaking, and pH adjustments, did not result in any additional fentanyl being extracted. This is discussed further in Section 11.

The used FSS spray devices are intended to be placed in an unlabeled sealable pouch that is disposed in the trash. Unused devices are to be disposed of in the pouch after the contents are sprayed into a (b) (4) disposal system. The system consists of a 100 cc plastic (HDPE) bottle (b) (4)

Each individual FSS unit will be enclosed in a child-resistant blister package. As reviewed by Dr. Reissig of the Controlled Substances Staff, in a test of 50 children (n=50), aged 42-51 months, the FSS package was found to be 98% child resistant.

The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 36 months is supported.

Dr. Pinto concluded that there were sufficient CMC data to assure the identity, strength, purity, and quality of the drug product, provided in the NDA submission. The drug substance manufacture and product attributes were referenced to DMF (b) (4) which was reviewed as Adequate (P. Maturu, June 2009 and J. Pinto, Rev #5, Oct 2011). The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product.

There were two outstanding deficiencies in the drug product stability protocol and stability specifications identified by Dr. Pinto in her initial review. The applicant has responded to information requests as noted below:

1. There are insufficient data to support the lack of testing for both weight loss and ethanol content for batches made at the (b) (4) (commercialization). (b) (4)

(b) (4). Therefore the following IR comments have been sent to the sponsor:

IR (4): There is insufficient commercial scale product history, to support the lack of testing for both weight loss and ethanol assay during stability. Maintain both the ethanol assay test and the weight loss test during routine stability testing. Further propose a release and stability specification for weight loss.

Response: The applicant agreed to continue to test both weight loss and ethanol assay during stability and provided updated specifications and a stability study protocol. Dr. Pinto found this response to be adequate.

IR(5): There is insufficient commercial scale product history, to support the (b) (4) proposed for stability testing. The first three production scale batches and a yearly production batch of the 4mg/ml intermediate strength is to be included in the stability study.

Response: The applicant has committed to testing the first three production scale batches and a yearly production batch of the 4mg/ml intermediate strength in the stability study. The annual stability batches will include the 1mg/ml, 4mg/ml and 8mg/ml batches. Dr. Pinto found this response to be adequate.

IR(6): (b) (4). Update the release and stability specifications to include testing for pH with data driven acceptance criterion.

Response: The applicant has added the pH testing parameter to the release and stability specifications. A pH range was not proposed as a specification, but will be added once sufficient data is collected on the full scale batches. Dr. Pinto found this response to be adequate.

In addition, she also notes the following deficiencies:

IR (3): The specification proposed for Spray Actuation Content is not in accordance with the FDA guidance for Nasal Sprays. Tighten the proposed specification to be in agreement with the FDA guidance (e.g., individual sprays to within ± 15 percent of the target weight and their mean weight to within ± 10 percent of the target weight).

Response: The applicant has requested to retain the currently proposed specification until data from the full scale batches become available. At that time, they commit to providing an update on the specification in the annual report. The current specification is (b) (4) Dr. Pinto found this response adequate as this is a single spray and the sponsor does not have sufficient data, this parameter can be evaluated once there is sufficient data.

The microbiology review by Dr. Riley notes that this product (b) (4) must meet microbial limits acceptance criteria at release. The initial acceptance criteria submitted by the applicant were (b) (4) the acceptance criteria for a liquid oral product suggested by USP, but the administered dose is small enough that the (b) (4) acceptance criteria are not of concern and are acceptable. Similarly, while aqueous drug products should have controls in place to ensure the absence of *Burkholderia cepacia*, since this product is (b) (4), there is no concern for *B. cepacia*.

A consultative review was conducted by LCDR Alan Stevens of CDRH. LCDR Stevens reviewed the device constituent for this Combination Product and provided an assessment of the Failure Modes and Effects Analysis. He found the following deficiencies:

1. You have provided a design failure modes and effects analysis. For each component, you have identified potential failure modes and associated causes. You claim to have identified design controls for each failure mode and, based on the analysis, conclude that no further mitigations are required. However, no design controls are identified. Instead, the dFMEA has identified manufacturing controls. Please modify the dFMEA to identify design controls and provide evidence that implementation of the design controls are effective.

Dr. Ryan reviewed the response from the applicant and found the dFMEA submitted was comprehensive and that all of the risk priority numbers fell within an acceptable range. The most common failures resulted in under dosing or no doses. The failures have a severity rating of three or less which Dr. Ryan notes is acceptable. She concludes the device issue is adequately resolved.

4. Nonclinical Pharmacology/Toxicology

The following is from Dr. Bolan's review.

The pharmacology and toxicology of fentanyl have been well characterized. No nonclinical toxicology studies were deemed necessary to characterize the safety of fentanyl for this product unless abnormalities arose during monitoring of pulmonary function in the clinical studies. No abnormalities in pulmonary function were noted in the clinical studies therefore, no nonclinical studies with fentanyl were conducted.

The excipients used in the FSS formulation are all found at higher levels in drugs previously approved by FDA and do not pose any toxicologic concerns. Extractable and leachable assessments were conducted with the (b) (4) FSS container closure system. Drug Master File (b) (4) for the (b) (4) is referenced by the Applicant. The (b) (4) are used in over 150 approved drugs, many with similar aqueous formulations to FSS. The Agency's previous finding of safety for the (b) (4) material will be relied on in order to support its safety.

The impurities/degradants in the drug substance and drug product are controlled at acceptable levels. A structural alert for mutagenicity was identified in the drug product degradant (b) (4). The Applicant conducted an Ames Assay which showed a negative result for mutagenicity, therefore (b) (4) can be regulated as a typical non-genotoxic impurity according to ICH Q3B(R2). The drug product specification set for (b) (4) in this NDA is acceptable.

There are no unique nonclinical issues associated with this product compared to the referenced fentanyl product. There are no outstanding concerns with this NDA that would preclude approval. The recommendation from Pharmacology/Toxicology is that NDA 202788 be approved with no post-marketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

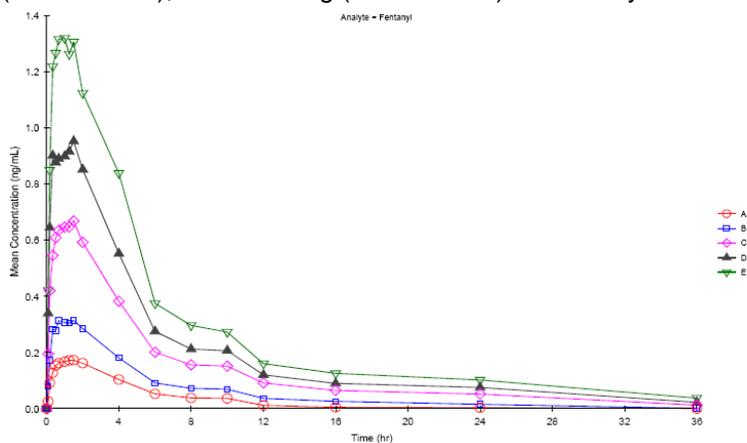
The applicant submitted four clinical pharmacology studies in support of this application. Three studies were in healthy subjects: a pilot, single ascending dose PK study, a single-dose relative bioavailability study (BA), and a single-dose, crossover, dose proportionality study that included an evaluation of the effects of temperature and pH. One study enrolled cancer patients to evaluate the effects of oral mucositis on PK.

As summarized by Dr. Qiu, fentanyl is highly lipophilic. The plasma protein binding is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4. Norfentanyl was not found to be pharmacologically active in animal studies. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in feces. The metabolites are mainly excreted in the urine.

As described by Dr. Qiu, the mean absolute bioavailability of Fentanyl Sublingual Spray 400 mcg in comparison to fentanyl citrate intravenous injection 100 mcg was 72.1% or AUC_{last} and 75.6% for AUC_{inf}, normalized for dose. One 400 mcg spray of FSS resulted in 34% and 36% greater C_{max} and AUC_{inf} values, respectively, compared to an Actiq dose of 400 mcg, under fasting conditions.

The average T_{max} ranged between 1.25 hours for the 100 mcg and 200 mcg doses to 0.67 hours for the 600 mcg dose. The mean half life was 5.25 hours for the 100 mcg dose, 8.45 hours for the 200 mcg dose, and up to 11.99 hours for the 800 mcg dose. While the half-life seems long for a drug intended to treat a breakthrough pain, the shape of the PK profile demonstrates a large early peak with a long tail as shown in the figure 1 (p. 8) from Dr. Qiu's review. The shape of the PK profile is compatible with the intended use of the product.

Figure 1 Mean Fentanyl Concentration-Time Profiles after Administration of Single Doses of Fentanyl Sublingual Spray 100 mcg (Treatment A), 200 mcg (Treatment B), 400 mcg (Treatment C), 600 mcg (Treatment D), and 800 mcg (Treatment E) from Study INS-06-004



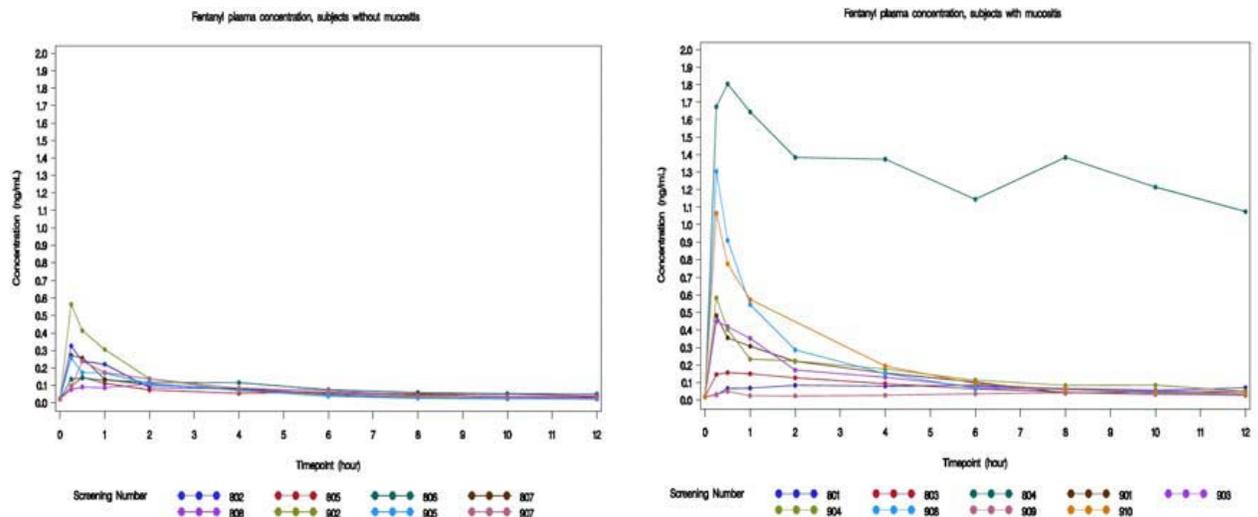
The systemic exposure of fentanyl increased in an approximately dose proportional manner over the 100 mcg to 800 mcg range, under fasting conditions based, on C_{max} and AUC, except for the lower bound of the 90% confidence interval which was slightly low for the C_{max} of the 600 mcg dose relative to the 800 mcg dose and for the 100 mcg and 200 mcg doses for AUC.

There was no clinically important effect from pre-treating the oral cavity with hot or cold water. There were small decreases in fentanyl exposure after pretreatment with a low pH beverage and small increases following a high pH beverage, but these were small enough to be of no clinical importance.

There were important findings in cancer patients with oral mucositis. In patients with Grade 1 mucositis, mean fentanyl C_{max} and AUClast values were 73% and 52% greater, respectively, than with patients without mucositis following the administration of a 100 mcg fentanyl sublingual spray.

Two patients with Grade 2 mucositis were studied. Fentanyl C_{max} values were 7-fold and 4-fold greater than the mean C_{max} values obtained in patients without mucositis for the two patients. However, the highest C_{max} in the Grade 2 mucositis patient was only 3-fold greater than the highest C_{max} in the group without mucositis. The corresponding fentanyl AUClast values were 17-fold and 3-fold higher than the average values in patients without mucositis. Figure 2 from Dr. Qiu’s review (p. 10) shows the individual PK profiles of patients without mucositis on the right and with mucositis on the left. In the figure on the left, the PK profile with the notably high fentanyl concentrations was from one of the patients with Grade 2 mucositis.

Figure 2. Fentanyl plasma concentration-time profiles in subjects without mucositis (left panel) and subjects with mucositis Grade 1 or 2 (right panel) from Study INS-09-011



Dr. Qiu recommended avoiding the use of fentanyl sublingual spray in patients with Grade 2 and worse mucositis and dose reduction should be done for the patients with Grade 1 mucositis. I agree with Dr. Qiu that there is no clinically important effect of temperature or

pH. Based on the information submitted with the original NDA, I also concurred that FSS should not be used by patients with Grade 2 mucositis or higher and that there should be a contraindication for this population. As the starting dose of FSS is 100 mcg, the lowest dose, there is no way to reduce the starting dose for patients with Grade 1 mucositis. However, as patients using FSS are meant to be opioid-tolerant, increased monitoring for respiratory and central nervous system depression when initiating dosing is sufficient to ensure patient safety.

(b) (4)

the applicant sought additional information about the patient with the 17-fold increase in AUC. According to additional information obtained after the investigator contacted the patient's family member, the patient brought Actiq to the study site and surreptitiously used the Actiq during the study. An amendment to the NDA was submitted December 20, 2011 documenting this. It is hard to understand exactly how a subject could use an Actiq dose without detection during a clinical pharmacology study, but the sustained fentanyl level over 12 hours does seem more compatible with additional dosing of a fentanyl product as an explanation. The mean oral bioavailability of FSS is approximately 70%. If mucositis resulted in a 100% exposure to the fentanyl, it would not result in a 17-fold increase in AUC. However, the fentanyl level was 0 at baseline and without more information, it is not possible to know whether the Cmax was influenced by the use of Actiq or not, and the Cmax was approximately 3-fold higher than the highest Cmax in the non-mucositis patients in the study. Given that the intended population is opioid-tolerant, and given that the patient with Grade 2 mucositis in question tolerated the high levels of fentanyl without respiratory depression, it seems reasonable not to contraindicate the use of FSS in patients with Grade 2 mucositis. In place of the recommendation will be a recommendation to avoid use of FSS in patients with Grade 2 mucositis or higher unless the benefit is expected to outweigh the possible risk of respiratory depression.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

With five approved products in the TIRF class, there has been a fair amount of experience with understanding the efficacy of these products. Fentanyl, a mu opioid agonist, is a known analgesic, available as intravenous, transmucosal and transdermal formulations. The current application relies on the Agency's prior findings of efficacy for Actiq, the listed drug referenced in the application, and one adequate and well controlled clinical trial. As FSS delivers fentanyl with a PK profile similar to Actiq, but not bioequivalent, the clinical trial was required to confirm that this new formulation provides efficacy in the intended population.

Drs. Yip and Zhou have reviewed Study INS-05-001 in detail. This was a multicenter, placebo-controlled, 10-period crossover study in opioid-tolerant cancer patients with breakthrough pain. Key inclusion criteria included adult patients with a diagnosis of cancer and persistent cancer pain or its treatment of moderate or less intensity, taking at least 25 mcg

of transdermal fentanyl per hour or 60 mg of oral morphine per day, 30 mg of oxycodone per day, 8 mg of oral hydromorphone or equivalent per day, around-the-clock, for at least one week, and, on average, one to four episodes of BTCP over the previous week at least partially controlled by supplemental medication of at least 5 mg immediate-release morphine or an equivalent short-acting opioid (e.g., oxycodone, hydrocodone, or acetaminophen with codeine.) Key exclusion criteria included the presence of painful erythema, edema or ulcers under the tongue, brain metastases, or clinically relevant abnormalities in vital signs, liver enzymes or serum creatinine. Concomitant use of CYP 3A4 inducers or inhibitors was prohibited.

Patients not using Actiq or Fentora prior to the study were titrated onto FSS according to the following algorithm:

- Start with the 100 mcg dose of FSS. Treat one episode of breakthrough pain.
- If this dose was effective and tolerated, the next episode of was treated with the same dose of FSS.
- If pain relief was inadequate after 30 minutes then the patient was to re-dose with one additional FSS dose.
- If the pain continued for 30 minutes following the re-dose, patients were instructed to take their usual analgesic medication as rescue medication.
- If a patient consistently required an additional 100 mcg of FSS at two subsequent breakthrough pain episodes, the patient proceeded to the next higher FSS dose strength, 200 mcg.

This continued until a successful dose was identified or a maximum dose of 1600 mcg (two 800 mcg sprays) failed to work and the patient then exited the study. Patients previously using Actiq or Fentora were allowed to begin on doses of FSS greater than 100 mcg based on their prior TIRF doses and then continued with titration according to the algorithm.

Patients were titrated to a successful dose, defined as a dose of FSS that consistently treated two consecutive breakthrough pain episodes and that was tolerated, and were supplied with a 10-dose drug pack containing 10 separate unit doses, marked 1 to 10. Patients were instructed to self-administer each dose, starting at unit dose 1 and working through to unit dose 10, in order, for each of 10 individual episodes of target breakthrough cancer pain. Patients were instructed to wait at least four hours between treated breakthrough pain episodes, and to treat no more than two breakthrough pain episodes with study drug in a given day.

One hundred and sixty-one patients were screened and 131 were enrolled in the study. One patient never received study drug. Of the 130 patients that entered titration, 32 (25%) withdrew prior to entering the double-blind crossover phase of the study. Dr. Yip explored the reasons for discontinuation during titration and the most common reasons were adverse events and inability to titrate to a successful dose.

A total of 45 patients were identified as having protocol violations. One patient (Subject 110003) was discontinued from the study during the titration period for a protocol violation. The patient was found to have lied about having cancer and, in fact, did not have cancer. The

patient was not included in the double-blind period. Two patients (Subject 110-007 and 110-006) were noted as not meeting the inclusion criterion of “experience persistent pain related to the cancer or its treatment of moderate or lesser intensity in the 24 hours prior to assessment by a verbal rating scale at the Screening Visit” and waivers were not granted for their participation. The Applicant was asked why the patients were enrolled and included in the study and queried the investigator. The response was that both patients had persistent cancer pain that was rated as severe at screening, but generally had pain of moderate intensity and so were enrolled. Based on this explanation, including these patients appears acceptable. The remaining violations were reviewed and were not sufficient to warrant discontinuation from the study.

Of the 98 patients who entered the double-blind period, three patients discontinued early, and 79 completed all 10 doses of blinded study drug. Patient disposition is presented in the following table from Dr. Zhou’s review.

Table 1 Patient Disposition

Table 2: Patient Disposition

	Number (%) of Patients
Screened	161
Titrated	130
Randomization	98 (100)
ITT*	96 (98)
Completed	95 (97)
Completed 10 episodes	79 (81)
Discontinued	3 (3)
Adverse events	1 (1)
not complied with protocol	1 (1)
Subject’s decision	1 (1)

Source: Reviewer’s Analyses

*Two subjects (114001, 119003) have no efficacy data due to an equipment malfunction

Source: Table 2 (p. 8) from Dr. Zhou’s review

The demographic characteristics of the study population are presented in the following table from Dr. Zhou’s review. As a crossover design, there were no concerns about imbalance across treatment groups. The study patients were mostly white and less than 65 years of age.

Table 2

Table 3: Baseline Demographic Characteristics for ITT population (N=96)

Age (years)	
Mean (SD)	54 (12)
Range	24-85
Age Group (years), n (%):	
< 65	80 (83%)
>=65	16 (17%)
Race, n (%)	
White	87 (91%)
Black or African American	7 (7%)
Native Hawaiian or Other Pacific Islander	1 (1%)
American Indian or Alaskan Native	1 (1%)
Other	1 (1%)
Gender, n (%)	
Female	52 (54%)
Male	44 (46%)

Source: Clinical Study Report Table 14.1.4

Source: Table 3 (p. 8) from Dr. Zhou's review

The final dose after titration ranged from 100 mcg to 1600 mcg. The distribution of final titrated dose is presented in the following table.

Table 3 Final titrated dose.

SUBSYS Dose	Total No. (%) n=96
100 mcg	4 (4%)
200 mcg	7 (7%)
400 mcg	14 (15%)
600 mcg	15(16%)
800 mcg	23 (24%)
1200 mcg	20 (21%)
1600 mcg	13 (14%)

The primary efficacy analysis was the summed pain intensity difference over 30 minutes (SPID30), based on the mean of the SPID30 across each episode for each treatment, i.e. the seven active-treated episodes were averaged and the three placebo-treated episodes were averaged. As noted by Dr. Zhou, her analysis differed from the applicants in that she included all 96 patients in the ITT population, regardless of the number of episodes treated and whether they were compliant with treatment order. Using the full ITT population, excluding data subsequent to the use of rescue medication, and using last observation carried forward to impute missing values, Dr. Zhou was able to replicate the applicant’s primary analysis and demonstrate that FSS was statistically superior in reducing pain intensity using the SPID30. The following table shows Dr. Zhou’s results from the primary efficacy analysis.

Table 4

Table 5: Reviewer’s Primary Efficacy Analysis

SPID30	Subsys Sublingual Spray (N of subjects = 93) (N of episodes = 632)	Placebo (N of subjects = 93) (N of episodes = 272)
LSMEANS (SE)	644 (41)	387 (45)
Difference from Placebo (SE)	257 (29)	
95% CI	(200, 315)	
P-value*	< 0.0001	

* P-value based on the ANOVA model with fixed effect treatment, episode, sequence and a random effect subject

Source: Table 5 (p. 10) from Dr. Zhou’s review

Dr. Zhou conducted subgroup analyses for gender and age. She found no statistically significant interaction between gender and treatment, although there was an interaction between age and treatment, with a smaller effect size for older patients. Statistically significant differences in favor of FSS for the SPID30 analysis remained for both groups, patients under the age of 65 and patients 65 years of age and older. These results are shown in the following table.

Table 5

Table 6: Reviewer's Subgroup Analyses for SPID30

Endpoint	Subsys		Placebo	
	n	Mean (SD)	n	Mean (SD)
SPID30				
Gender				
Female	50	621 (514)	50	401 (493)
Male	43	667 (634)	43	388 (529)
Age (years)				
< 65	77	667 (594)	77	390 (521)
≥ 65	16	525 (447)	16	415 (453)

Source: Table 6 (p. 11) from Dr. Zhou's review

There were too few non-white patients (13%) for a meaningful subgroup analysis based on race.

The secondary efficacy analyses included total pain relief at 30 minutes (TOTPAR30) and Patient Global Evaluation of Study Medication at 30 minutes. These analyses found statistically significant difference between active and placebo treatments in favor of the active drug. Additional analyses of SPID and TOTPAR at 5, 10, 15, 45 and 60 minutes were conducted by the applicant on an evaluable population of 92 patients. The applicant claimed these were statistically significantly different between treatments and favored active drug, however, these evaluations were not corrected for multiplicity and were not repeated with the full ITT population as they are not included in labeling.

In addition, the use of rescue medication was examined by the applicant. Among the evaluable population, rescue medication was used by patients during 28% of episodes treated by placebo compared to 10% of episodes treated by active drug.

Overall, Study INS-05-001 was successful in demonstrating the efficacy of FSS in reducing breakthrough pain in opioid-tolerant cancer patients.

8. Safety

The applicant describes 490 subjects exposed to FSS and making up the safety database, however 107 patients from two PK studies were pretreated with naltrexone and so, would not have been able to contribute safety data other than local reactions. Study INS-09-011 was a single dose study of FSS in cancer patients evaluating the effects of mucositis enrolling 18 subjects. The primary safety database is based on studies INS-05-001 (Study 001), the efficacy study, and INS-06-007 (Study 007), an open-label safety study lasting up to 90 days that rolled patients over from Study 001 and enrolled novel patients. There were 359 subjects who took a least one dose of FSS from these two studies that contributed to the safety database. The 359 patients represent 130 patients who underwent titration and 98 who entered the double-blind period of Study 001, 90 who rolled over from Study 001 to Study 007, and 179 novel patients who enrolled in Study 007.

The extent of exposure from Studies 001 and 007 is presented in the following table from the applicant:

Table 6

Table 1.2
Summary of Subject Disposition by Duration of Dosing
Phase 3 Studies (Study INS-05-001 and INS-06-007)
Safety Population (N = 359)

	Day 1 to 1 month	1 to 2 months	2 to 3 months	> 3 months	Total (N=359)
Entering and Terminated Fentanyl SL Spray in this Period	111	38	35	175	359
Completed the Period	4 (3.6%)	1 (2.6%)	1 (2.9%)	162 (92.6%)	168 (46.8%)
Early Terminated from the Period	107 (96.4%)	37 (97.4%)	34 (97.1%)	13 (7.4%)	191 (53.2%)
Unable to Determine a Successful Dose During the Titration Period	5 (4.5%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	6 (1.7%)
Intercurrent Illness, AE or Surgery	11 (9.9%)	2 (5.3%)	4 (11.4%)	2 (1.1%)	19 (5.3%)
AEs and SAEs that Contraindicate Further Administration of the Study Drug	30 (27.0%)	22 (57.9%)	22 (62.9%)	5 (2.9%)	79 (22.0%)
Symptoms or Signs Indicating Possible Toxicity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Failure to Comply with Administrative Requirements of the Protocol	4 (3.6%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	6 (1.7%)
Significant Protocol Violation	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Investigator Decision	6 (5.4%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	8 (2.2%)
Sponsor Decision	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Subject Decision for Withdrawal	41 (36.9%)	10 (26.3%)	3 (8.6%)	4 (2.3%)	58 (16.2%)
Other	6 (5.4%)	2 (5.3%)	3 (8.6%)	0 (0.0%)	11 (3.1%)

Note: Subjects are counted only once in each period. Termination is defined by the latest period in the study. Subjects 231004 and 235009 had partial last dose date. In order to define the duration of dosing the last day of the month was imputed.

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This database is sufficient in size to evaluate the safety of the FSS formulation, in conjunction with what is already known about the safety of fentanyl. Among these patients, nearly half were treated for at least three months or longer. The most common reason for discontinuing FSS throughout the studies was adverse event. As a cancer patient population on around-the-clock opioids, opioid-related adverse events are expected. The addition of FSS could be expected to exacerbate opioid-related adverse events. The population would also be expected to have adverse events related to their underlying cancers.

The five most common cancer types in this population were lung (19.2%), reproductive (17.5%), breast (15.0%), head and neck (12.8%) and colorectal (10.3%). The mean duration of cancer was 5.5 years, with similar durations within the ranges <1 year, 1-5 years, and >5 years. Most cancers were stage 4 (42.3%) or stage 3 (18.1%), and most had prior or concurrent radiation (63.5%), surgery (74.7%) or chemotherapy (80.8%).

The overall incidence of adverse events was 88% of the 359 patients, totaling 1921 events. The applicant reported that 44.8% of patients had treatment-related events.

Deaths

There were 92 deaths during the clinical studies. The ISS reports 85 deaths, although the total based on the two studies, Study 005 and Study 007, adds up to 92. The applicant explained the

different numbers based on the reporting periods. For the ISS, events during the study or within 30 days were reported. For the individual studies, all events, even those later than 30 days from the end of the study were reported, and seven of the deaths occurred later than 30 days after the last administration of study medication. One death was attributed as treatment-related according to the applicant. The dose of FSS and the number of patients who died and had SAEs and early withdrawal due to an AE is provided in the following table from the ISS. There were proportionately more deaths among patients taking the highest dose of FSS, but this may reflect worse underlying disease.

Table 7

Table 6
Summary of Overall Treatment-Emergent Adverse Event (TEAE) Information
Phase 3 Studies (Study INS-05-001 and INS-06-007)
Safety Population (N = 359)

Dose Level (mcg):	100 (N=350)	200 (N=294)	400 (N=239)	600 (N=175)
Number of Subjects Who had a TEAE with an Outcome of Death	25 (7.1%)	16 (5.4%)	10 (4.2%)	8 (4.6%)
Number of Subjects Who had a Treatment-Related TEAE with an Outcome of Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of Subjects Who had a TEAE Leading to Withdrawal from Study	20 (5.7%)	10 (3.4%)	8 (3.3%)	6 (3.4%)
Number of Subjects Who had a Treatment-Related TEAE Leading to Withdrawal from Study	9 (2.6%)	4 (1.4%)	2 (0.8%)	2 (1.1%)
Dose Level (mcg):	800 (N=139)	1200 (N=90)	1600 (N=50)	Total (N=359)
Number of Subjects Who had a TEAE with an Outcome of Death	12 (8.6%)	7 (7.8%)	7 (14.0%)	85 (23.7%)
Number of Subjects Who had a Treatment-Related TEAE with an Outcome of Death	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Number of Subjects Who had a TEAE Leading to Withdrawal from Study	8 (5.8%)	10 (11.1%)	6 (12.0%)	63 (17.5%)
Number of Subjects Who had a Treatment-Related TEAE Leading to Withdrawal from Study	2 (1.4%)	3 (3.3%)	2 (4.0%)	22 (6.1%)

Dr. Yip reviewed the narratives for patients who died during the clinical trials. During Study 001, there were three deaths. One patient with metastatic lung cancer started titration on FSS and was admitted to the hospital with evidence of advancing metastatic disease of the spine, one week after starting study drug. He died three weeks later without further exposure to study drug. The second patient had pancreatic cancer and died at least two weeks after his single exposure to study drug. The third patient had cervical cancer. She titrated to the 1600 mcg dose of study drug and entered the double-blind period. She was admitted to hospice care and died two weeks later and the last date of study drug dosing was not reported. The first two cases were clearly unrelated to study drug. Given that the third patient tolerated the drug during titration and entered the double-blind period, it is unlikely that her death during hospice care was related to study drug.

Of the remaining 89 deaths during Study 007, Dr. Yip summarized his review as follows:

The CRFs, data listings, and narratives were reviewed for each death. There were 77 patients who died of cancer progression and 12 who died of other reasons: sepsis (2),

pulmonary embolism (2), cardiopulmonary arrest, cardiac failure, cardiac arrhythmia, aspiration pneumonia, intracranial hemorrhage, stroke, renal failure, and respiratory distress (aspiration). Of the 12 patients who died of other reasons, eight appeared to have died as a result of underlying malignancy, progression of disease, complications of the underlying disease, treatments, concomitant medications, or other events surrounding the AEs (i.e., sepsis (2), pulmonary embolism (2), heart failure, intracranial hemorrhage, stroke, and renal failure) and unrelated to study participation.

He identified several deaths for closer inspection. Patient 142009 died after developing aspiration pneumonia which can occur as a result of opioid-induced respiratory depression, but the patient had been tolerating study drug throughout the efficacy study and two weeks of the safety study, so this seems unlikely. Patient 413007 died several days after her last dose of study drug. Patient 400006 died a day after her last dose of study drug, after leaving the hospital against medical advice. It is unlikely that study drug contributed to either of these deaths.

Patient 408004 had a history of lung cancer with brain and liver metastases. He titrated to 100 mcg of FSS and entered the maintenance period. On Study Day 24, the patient developed diarrhea. On Study Day 25, he vomited and collapsed, and died approximately 90 minutes after the last dose of study drug. An autopsy was not performed and a death certificate was not available. The pharmacokinetic characteristics of fentanyl administered as FSS suggest that, at the time of death, fentanyl levels were past the maximum concentration and effect. Although the contribution of study drug to patient death cannot be excluded, the patient had tolerated study drug for 25 days and it seems more likely that he died as a result of a catastrophic event related to his underlying malignancy.

Patient 411002 had a history of stomach cancer associated with dysphagia, anorexia, and ascites. The patient died 14 days after initiating treatment with study drug, and her last FSS dose was two hours prior to her death. There were few details provided about the events surrounding her death, and based on the timing of study drug, a contribution to the patient's death cannot be excluded. However, having tolerated the drug for 14 days makes a direct effect of study drug unlikely.

Patient 142013 had a history of head and neck cancer. The patient was rolled over from study INS-05-001 and entered the maintenance period on (b) (6) using a FSS dose of 1200 mcg. On (b) (6) the subject died as a result of asystole associated with cardiac arrhythmia. The SAE was evaluated by the investigator as severe and possibly related to study medication. Fentanyl by intravenous route has been associated with bradyarrhythmias, so it is possible that fentanyl from study drug may have contributed to this death.

Serious Adverse Events

There were 211 serious adverse events reported in 130 of the subjects including the deaths. Of the remaining including 4 treatment related events in three subjects. There were 59 subjects out of the 359 who had non-fatal serious adverse events. The most common serious adverse events were progression of malignant neoplasm, anemia, pneumonia, cancer pain, nausea, neutropenic colitis, vomiting, and dyspnea. There were also serious cases of fatigue,

leukopenia, thrombocytopenia, tachycardia, electrolyte imbalance, peripheral edema, deep vein thrombosis, diarrhea and gastritis. In this population of cancer patients receiving a variety of treatments for the underlying cancer, it is very difficult to assign causality or exclude causality between use of FSS and events such as nausea, vomiting, electrolyte imbalance, dyspnea and fatigue. There are no data to suggest that fentanyl contributes to cancer progression, pneumonia, or bone marrow suppression.

Table 8 Study INS-05-001

Table 12-8: Incidence of serious adverse events by preferred term

Preferred Term	Titration Period	Double-Blind Period
	(N=130) n (%)	(N=98) n (%)
Any SAE	7 (5.4)	6 (6.1)
Abdominal Pain	1 (0.8)	1 (1.0)
Cellulitis	1 (0.8)	1 (1.0)
Fistula	1 (0.8)	—
Gastroenteritis Viral	—	1 (1.0)
Hyponatraemia	1 (0.8)	—
Leukopenia	1 (0.8)	—
Lung Cancer Metastatic	1 (0.8)	—
Malignant Neoplasm Progression	1 (0.8)	1 (1.0)
Metastases To Bone	1 (0.8)	—
Nausea	1 (0.8)	1 (1.0)
Paraplegia	—	1 (1.0)
Spinal Cord Neoplasm	1 (0.8)	—
Tachycardia	—	1 (1.0)
Vomiting	1 (0.8)	1 (1.0)

Source: Table 14.3.12 and 14.3.13

Table 9 Study INS-06-007

Table 12-11: Incidence of serious adverse events other than death occurring in more than one subject during either period by preferred term

Preferred Term	Titration Period	Maintenance Period
	(N=229) n (%)	(N=269) n (%)
Malignant Neoplasm Progression	5 (2.2%)	60 (22.3%)
Disease Progression	2 (0.9%)	5 (1.9%)
Anaemia	NA	4 (1.5%)
Pneumonia	NA	4 (1.5%)
Cancer Pain	NA	4 (1.5%)
Nausea	1 (0.4%)	3 (1.1%)
Neutropenic Colitis	NA	3 (1.1%)
Vomiting	2 (0.9%)	3 (1.1%)
Non-Small Cell Lung Cancer	2 (0.9%)	3 (1.1%)
Prostate Cancer	1 (0.4%)	3 (1.1%)
Dyspnoea	NA	3 (1.1%)
Cellulitis	NA	3 (1.1%)
Pulmonary Embolism	1 (0.4%)	3 (1.1%)
Thrombocytopenia	NA	2 (0.7%)
Abdominal Pain	1 (0.4%)	2 (0.7%)
Fatigue	NA	2 (0.7%)
Oedema Peripheral	NA	2 (0.7%)
Diarrhoea	NA	2 (0.7%)
Gastritis	NA	2 (0.7%)
Electrolyte Imbalance	NA	2 (0.7%)
Deep Vein Thrombosis	NA	2 (0.7%)

NA=Not applicable; SAEs of this preferred term did not occur during this period

Sources: Section 14, Table 14.3.2.1A and Table 14.3.2.1B

Discontinuations due to Adverse Events

A total of 67/359 (19%) patients from studies INS-05-001 and INS-06-007 discontinued study medication due to AEs; 9/359 (3%) patients discontinued study medication during study INS-05-001 and 58/359 (16%) patients discontinued study medication during study INS-06-007.

Dr. Yip reviewed the CRFs, narratives, and datasets provided by the Applicant. The most common AEs leading to early discontinuation are provided in the following table from the applicant. Nausea, anorexia, abdominal distention, confusional state, constipation, disorientation, headache, mood swings, paranoia, and somnolence are all known effects of opioids and may have been related to study drug. The oral pain is specific to this type of formulation. The CRF of the patient reporting oral pain leading to discontinuation was reviewed by Dr. Yip and this appears to have been related to study drug.

Table 10 Withdrawal From the Study by Preferred Term - Phase 3 Studies (Study INS-05-001 and INS-06-007)

Preferred term	Total (N=359)	%
Any adverse event	63	(17.5%)
Malignant neoplasm progression	23	(6.4%)
Nausea	5	(1.4%)
Constipation	3	(0.8%)
Diarrhea	3	(0.8%)
Disease progression	3	(0.8%)
Somnolence	3	(0.8%)
Vomiting	3	(0.8%)
Abdominal distension	2	(0.6%)
Anorexia	2	(0.6%)
Application site irritation	2	(0.6%)
Cancer pain	2	(0.6%)
Confusional state	2	(0.6%)
Depression	2	(0.6%)
Dyspnea	2	(0.6%)
Euphoric mood	2	(0.6%)
Hyponatremia	2	(0.6%)
Non-small cell lung cancer	2	(0.6%)
Pneumonia	2	(0.6%)
Abscess	1	(0.3%)
Acute respiratory distress syndrome	1	(0.3%)
Amnesia	1	(0.3%)
Anaemia	1	(0.3%)
Asthenia	1	(0.3%)
Bladder cancer	1	(0.3%)
Cheilitis	1	(0.3%)
Chest discomfort	1	(0.3%)
Colon cancer metastatic	1	(0.3%)
Decubitus ulcer	1	(0.3%)
Depressed level of consciousness	1	(0.3%)
Disorientation	1	(0.3%)
Dysuria	1	(0.3%)
Feeling drunk	1	(0.3%)
Flatulence	1	(0.3%)
Gastric ulcer	1	(0.3%)
Hematemesis	1	(0.3%)
Headache	1	(0.3%)
Hepatic enzyme increased	1	(0.3%)
Hyperchlorhydria	1	(0.3%)
Hypokalemia	1	(0.3%)
Lung cancer metastatic	1	(0.3%)
Mood swings	1	(0.3%)
Myelodysplastic syndrome	1	(0.3%)
Edema peripheral	1	(0.3%)
Oral pain	1	(0.3%)
Panic attack	1	(0.3%)
Paranoia	1	(0.3%)
Prostate cancer	1	(0.3%)
Pyrexia	1	(0.3%)

Table 10 continued

Rash papular	1	(0.3%)
Respiratory distress	1	(0.3%)
Septic shock	1	(0.3%)
Spinal cord neoplasm	1	(0.3%)
Stomatitis	1	(0.3%)
Thrombocythemia	1	(0.3%)
Tongue injury	1	(0.3%)
Tooth infection	1	(0.3%)
Visual disturbance	1	(0.3%)

Note: Subjects are counted once within each preferred term.

All investigator adverse event terms were coded using MedDRA Dictionary Version 10.1.

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Common Adverse Events

Based on the safety population from Studies 001 and 007, the most common non-serious adverse events were nausea, constipation, dizziness, and somnolence. The applicant provided the following table of adverse events identified as being of particular clinical interest, although without providing the criteria for selection of the adverse events.

Table 11. Applicant's Table of Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Titration in the Clinical Trials (Events in 1% or More of Patients)

System Organ Class	Titration n=359 (%)	After Titration N=269 (%)
Gastrointestinal Disorders		
Nausea	47 (13.1%)	28 (10.4%)
Vomiting	37 (10.3%)	43 (16.0%)
Constipation	18 (5.0%)	28 (10.4%)
Dry Mouth	7 (1.9%)	
Nervous System Disorders		
Somnolence	34 (9.5%)	10 (3.7%)
Dizziness	26 (7.2%)	3 (1.1%)
Headache	13 (3.6%)	6 (2.2%)
General Disorders and Administration Site		
Asthenia	8 (2.2%)	26 (9.7%)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	11 (3.1%)	28 (10.4%)
Psychiatric Disorders		
Anxiety		16 (5.9%)
Confusional State	9 (2.5%)	12 (4.5%)
Hallucination	5 (1.4%)	5 (1.5%)
Insomnia	4 (1.1%)	12 (4.5%)
Disorientation		3 (1.1%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	5 (1.4%)	4 (1.5%)
Hyperhidrosis		4 (1.5%)

A full listing of treatment emergent adverse events was requested of the applicant and is provided in Appendix 1. The following table represents adverse reactions in the safety population occurring in one percent or more of patients.

Table 12 Adverse Reactions by preferred term, descending frequency, safety population Studies INS-05-001 and INS-06-007

Preferred Term	Total N=359	%
Any Adverse Event	316	(88%)
Nausea	79	(22.0%)
Vomiting	78	(21.7%)
Constipation	45	(12.5%)
Edema peripheral	43	(12.0%)
Somnolence	41	(11.4%)
Dyspnea	38	(10.6%)
Asthenia	35	(9.7%)
Fatigue	33	(9.2%)
Dizziness	29	(8.1%)
Application site irritation	23	(6.4%)
Anxiety	21	(5.8%)
Anemia	20	(5.6%)
Back pain	20	(5.6%)
Confusional state	20	(5.6%)
Headache	20	(5.6%)
Cough	19	(5.3%)
Stomatitis	18	(5.0%)
Anorexia	17	(4.7%)
Dehydration	16	(4.5%)
Depression	13	(3.6%)
Abdominal pain	12	(3.3%)
Pain in extremity	12	(3.3%)
Arthralgia	11	(3.1%)
Decreased appetite	11	(3.1%)
Dry mouth	10	(2.8%)
Hallucination	10	(2.8%)
Hyperhidrosis	10	(2.8%)
Muscular weakness	10	(2.8%)
Pruritus	10	(2.8%)
Sedation	10	(2.8%)
Dysphagia	9	(2.5%)
Hypertension	9	(2.5%)
Lethargy	9	(2.5%)
Restlessness	9	(2.5%)
Tachycardia	9	(2.5%)
Dysuria	8	(2.2%)
Gastritis	8	(2.2%)
Abdominal distension	7	(1.9%)
Abdominal pain upper	7	(1.9%)
Agitation	7	(1.9%)
Fall	7	(1.9%)
Pharyngolaryngeal pain	7	(1.9%)
Tremor	7	(1.9%)
Urinary retention	7	(1.9%)

Table 12 continued

Hypotension	6	(1.7%)
Rash erythematous	6	(1.7%)
Chills	5	(1.4%)
Disorientation	5	(1.4%)
Dysgeusia	5	(1.4%)
Dyspepsia	5	(1.4%)
Leukopenia	5	(1.4%)
Lymphadenopathy	5	(1.4%)
Malaise	5	(1.4%)
Musculoskeletal pain	5	(1.4%)
Thrombocytopenia	5	(1.4%)
Vision blurred	5	(1.4%)
Abdominal pain lower	4	(1.1%)
Blood alkaline phosphatase increased	4	(1.1%)
Blood lactate dehydrogenase increased	4	(1.1%)
Chest pain	4	(1.1%)
Drug withdrawal syndrome	4	(1.1%)
Dysphonia	4	(1.1%)
Hiccups	4	(1.1%)
Odynophagia	4	(1.1%)

Source Amendment to NDA dated 12/21/11

Overall, the adverse event profile described by the safety database is consistent with the delivery of an opioid. The adverse events reported reflect the effects of study drug, but also reflect that this was a population with active cancer causing pain, taking around-the-clock opioids and many other medications. There are no data that suggest dosing with FSS results in unexpected findings. Titration, as carried out in the study, did not result in overdoses. There was one death possibly associated with a dose of FSS, a patient who developed asystole. Fentanyl is known to be associated with bradyarrhythmias, although the patient was very ill and may have had other reasons for a cardiac arrest. The serious adverse events, adverse events leading to discontinuation and common adverse events did not include any safety signals that require additional data prior to marketing of this product.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application as no novel issues arose.

10. Pediatrics

The applicant requested a full waiver for studies under the Pediatric Research Equity Act in patients for the indication of management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer because there are too few children with disease/condition to study. This

request was reviewed by the PeRC PREA Subcommittee on December 7, 2011 which agreed that the studies were not feasible and granted a full waiver for this product.

11. Other Relevant Regulatory Issues

Consultative Review by the Controlled Substances Staff

The Controlled Substances Staff was consulted and a review was performed by Dr. Chad Reissig. He noted concern about the residual (b) (4) of drug solution that remains in the device after actuation. Dr. Reissig calculated a worst case scenario in which the full (b) (4) of 800 mcg/(b) (4) solution could be collected from 28 devices yielding (b) (4) of fentanyl. Dr. Reissig reviewed a study (Study CHP10010) to determine the amount of fentanyl that actually could be recovered from a used FSS device. The conditions studied included:

- Crushing the vial wrapped in a cloth then orally absorbing the residual fentanyl by placing the cloth in the mouth.
- Using a nail, screw, paperclip, or needle to remove the stopper, then chewing the stopper.
- Using a syringe to extract residual medication from the vial for the purpose of obtaining fentanyl for injection.
- Heating the device using common kitchen appliances (a microwave, pot of boiling water, and oven) to disassemble the sprayer and access to the medication.
- Using a flame from a lighter or candle to inhale medication from a disassembled sprayer.
- Applying suction on the nozzle by sucking on the device.

The syringe netted the most recoverable fentanyl with maximum of 42.7% of the residual fentanyl which would represent about (b) (4) mcg/device at the maximum FSS dose.

The applicant also conducted two extraction studies to determine the amount of fentanyl that can be retrieved from the (b) (4) disposal system. In one study, (b) (4) were weighed into a bottle and 28 800 mcg-devices were actuated into the bottle delivering a total of (b) (4) of fentanyl. Eight separate techniques were studied:

1. Overnight alcohol heating extraction
2. Overnight water heating extraction
3. Water extraction
4. Alcohol extraction
5. Alcohol heating extraction
6. Water heating extraction.
7. Consumable ethanol extraction study (i.e. Bacardi Rum)
8. Isopropyl alcohol extraction

The greatest amount of fentanyl that could be extracted from the (b) (4) was (b) (4), approximately 6%, using isopropyl alcohol.

In the second study, the same amount of fentanyl was delivered to the [REDACTED] (b) (4) bottle. Fentanyl recovery was measured after 1, 3, 6, and 12 hours after the following extraction conditions:

1. Dehydrated alcohol, isopropanol, and ethyl acetate
 - a. At room temperature with agitation
 - b. Heated to 70°C with agitation
2. Acetone and methanol
 - a. At room temperature with agitation
 - b. Heated to 50°C with agitation
3. Water, 6N HCl, and 6N NaOH
 - a. At room temperature with agitation
 - b. Heated to 90°C with agitation

The greatest extraction of fentanyl from this group of conditions was afforded [REDACTED] (b) (4) of fentanyl (1.23%) using dehydrated alcohol at room temperature for 1 hour. Serial extractions yielded [REDACTED] (b) (4) mg of fentanyl using isopropanol at room temperature over a course of 12 hours. Dr. Reissig concluded the [REDACTED] (b) (4) disposal system is adequate.

Dr. Reissig disagreed with the applicant's assertion that [REDACTED] (b) (4). He also noted that it appears as though it would be easy to draw fentanyl solution into a needle for the purpose of injection.

Reviewing the clinical studies for evidence of intentional abuse and misuse, Dr. Reissig noted that:

Overall, 87,632 units were dispensed across the two trials and 1,223 were not returned (1.4%). Of the 359 unique subjects, 77 did not return at least one device (21%). A total of 26 subjects were discontinued from the pivotal studies. Seven subjects were discontinued due to "failure to comply with the administrative requirements of the protocol". Two subjects were discontinued due to a "significant protocol violation". Six subjects were discontinued due to "unable to determine a successful dose during titration". Eleven subjects were discontinued due to "other". According to the Sponsor, 24 of the 26 patients returned 100% of their study medication. One subject (subject 222-002) was discontinued for being under the influence of narcotics. The CRF was unclear as to whether "narcotics" included the study drug.

There was also one patient identified during Study INS-05-001 who lied about having cancer and was discontinued from the study during the open-label titration.

Dr. Reissig reviewed a focus group study, (study INS-10-013) during which participants were provided a used FSS device and asked to identify it. Subjects produced 83 different ideas, including identifying the FSS device as a medical product, personal grooming product, childcare device, toy, food/candy dispenser, and safety device. In addition, the same study found that individuals were incapable of distinguishing used (actuated or spent) devices from unused product, and that children identified the device as candy.

Dr. Reissing concluded the following:

From an abuse potential perspective, the major risk associated with FSS is inadvertent exposure or dosing of children, pets, and unsuspecting individuals. The FSS unit appears innocuous and benign. The non-harmful appearance of FSS may result in, mishandling (e.g., accidental discharge) or careless disposal. Prominent labeling on the FSS device may decrease the risk that a device will be unattended to or unaccounted for, and decrease the risk of accidental exposure of FSS (both used and unused devices) to children, pets, and individuals.

He also concluded:

There is also the risk of manipulation of the product (e.g. disassembly) for the purpose of injection. The sample units received by the reviewer were easy to take apart and separate into individual components. Separating the FSS unit into individual parts reveals an “injection ready” fentanyl solution that does not require preparation (i.e. extraction or purification) prior to i.v. administration. The fentanyl solution is highly attractive to a drug abuser, conferring a high abuse potential to FSS.

Based on the attractiveness of the fentanyl solution, we recommend the Sponsor redesign the FSS unit so that manipulation and disassembly of the FSS device is more difficult, and the FSS device is more secure.

Dr. Reissig recommended that the FSS unit be redesigned to make disassembly more difficult for those who wish access to the solution for intravenous administration. However, even were the spray devices impenetrable, the solution could be sprayed into syringe if desired. The currently marketed oral TIRF products are all easily dissolved and the nasal spray is also a solution so it is unclear whether Dr. Reissig believed that the fentanyl in an FSS unit is appreciably easier to access for abuse by the intravenous route of administration than other fentanyl products already approved and marketed in the U.S. or would just prefer that the design be more robust. The REMS under which FSS will be approved will require enrollment of the prescriber, patient, and pharmacy. There are strong educational components for the prescriber and patient to teach them about the proper use, handling and disposal of FSS and about the risks of overdose and death for patients and household contacts if the proper procedures are not followed. There is a medication guide and instructions for use that the patient will have at home reminding them of the proper handling and disposal of the product along with the risks of not complying with the instructions. Each spray unit is packaged in a child-resistant pouch. Therefore, I disagree that the device must be redesigned. After further discussion, Dr. Reissig amended his recommendations to the following:

Initial concerns of this reviewer were based on personal observation of how easily the FSS sample device provided by the Sponsor could be disassembled, thus presenting a potential accidental exposure risk to children and pets. However, based upon the conclusions stated in the final Chemistry review (DARRTS, NDA 202-788, Julia C. Pinto, November 21, 2011), that the product attributes are adequate and the device meets CMC requirements, I retract my prior recommendation. Thus, the Sponsor does not need to improve the construction of the FSS device.

It is necessary to ensure that the individual devices are adequately labeled and identifiable. The device should never be out of the child resistant packaging prior to use and the used device should always be placed in the disposal pouch after use. There should never be a situation when it is critical to determine visually whether a device has been actuated or not. Comments from DMEPA about labeling were sent to the applicant who amended their labeling accordingly.

REMS

FSS will be available only through a restricted program under a REMS called the TIRF REMS ACCESS program. Under the TIRF REMS ACCESS program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of Subsys, patient and prescriber enrollment is not required.

Required components of the TIRF REMS ACCESS program are:

- Healthcare professionals who prescribe Subsys must review the prescriber educational materials for the TIRF REMS ACCESS program, enroll in the program, and agree to comply with the REMS requirements.
- To receive Subsys, patients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense Subsys must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute Subsys must enroll in the program and distribute only to authorized pharmacies.

Clinical Site Inspections

The Division of Scientific Investigations evaluated three clinical sites for Study INS-05-001. Two sites were classified as no action indicated as no deviation from regulations was found. The third site, W. Keith Lara, MD, 195 Commons Loop, Suite F, Kalispell, MT, was classified as voluntary action indicated due to some deviations. A Form FDA 483 was issued for: (1) not having the Delegation of Authority adequately documented for 3 study personnel, (2) not reporting 3 protocol deviations (2 dosing errors, 1 instance of not completing the Treatment Satisfaction Questionnaire for Medication) to the IRB, and (3) failing to re-obtain informed consent from one subject after revision of the consent form using the most recent IRB-approved version. The Form FDA 483 observations are considered minor deficiencies that appeared to be isolated instances, which are not expected to affect the study outcome. Overall, data from this study site appear reliable and to have been accurately reported in the NDA.

Patent Certification

The Applicant has provided Paragraph II Certification, and certified, to the best of its knowledge, that there are no unexpired patents for the Reference Listed Drug, ACTIQ (NDA 20-747), listed in the Orange Book Database (accessed online on December 21,2011).

Financial Disclosure

Dr. Yip reviewed the financial disclosure reported by the applicant and found no areas of concern.

12. Labeling

A proprietary name review by Dr. Anne Tobenkin of DMEPA of the proposed proprietary name, Subsys, did not identify any vulnerabilities that would result in medication errors with the additional names noted in this review. Thus, DMEPA has no objection to the proprietary name, Subsys, for this product at this time.

DMEPA also provided an evaluation of both the labels and labeling as well as the Label Comprehension and the Design Failure Mode and Effects Analysis (DFMEA) for medication error potential and usability of the device in the usual practice setting. Several safety issues were identified such as the controlled substance statement and ingredient per unit were not communicated on the labels and labeling which may cause confusion during use of the product and result in medication errors. Recommendations to mitigate confusion were communicated to the applicant and were incorporated in updated labeling.

DMEPA also found that the submitted studies identified problems with several stages of device use and determined that the provided instructions resulted in confusion during dosing. Although the instructions were revised as a result of the identified confusion, testing of the revised instructions on a new population was recommended to ensure they adequately communicate safe instructions for use. This testing was conducted and the reviewed instructions and results from the study are acceptable.

The medication guide and instructions for use were reviewed by members of the Division of Medical Policy Programs in the Office of Medical Policy Initiatives. Edits were requested of and agreed to by the applicant.

The carton and container labels were reviewed by DMEPA.

Although patients entering the study who had been on Actiq or Fentora were converted to a starting dose based on the dose of Actiq or Fentora that had been used, with the proliferation of TIRF products, and the differences in bioavailability across the group of products, it is safest for prescribers to initiate therapy with FSS with the 100 mcg dose and titrate from there to the dose that provides adequate analgesia and tolerable side effects.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action - Approval
- Risk Benefit Assessment

There is adequate evidence of efficacy for FSS based on the clinical study performed and reliance on the Agency's prior findings of efficacy for Actiq. The safety profile from clinical trials appears to be adequately balanced by the efficacy in conjunction with the REMS. As discussed above, transmucosal immediate-release fentanyl products require a REMS to ensure that the benefits outweigh the risks of overdose and death. FSS has the potential for causing overdose and death in patients who use the product incorrectly, in inappropriately selected

patients, particularly patients who are not already opioid-tolerant, in the setting of accidental exposure and in the setting of intentional abuse and misuse. However, opioid-tolerant cancer patients with breakthrough pain have benefited from having this class of drug available. There is great inter-individual variability in exposure with these products so having another option that is different in formulation, in this case a sublingual spray, is helpful to patients. The REMS is intended to ensure that prescribers, pharmacists, and patients and their caregivers are all properly educated about the risks and safe use of the product including how to properly dispose of the used and unused spray devices.

- Recommendation for Postmarketing Risk Management Activities

Subsys will be available only through a restricted program under TIRF REMS ACCESS program. Under the TIRF REMS ACCESS program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of Subsys, patient and prescriber enrollment is not required.

Required components of the TIRF REMS ACCESS program are:

- Healthcare professionals who prescribe Subsys must review the prescriber educational materials for the TIRF REMS ACCESS program, enroll in the program, and agree to comply with the REMS requirements.
- To receive Subsys, patients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense Subsys must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute Subsys must enroll in the program and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at www.tirfremssaccess.com or by calling 1-866-822-1483.

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

None

Appendix 1

Common Treatment Emergent Adverse Events by preferred term, descending frequency, safety population Studies INS-05-001 and INS-06-007

Preferred Term	Total N=359	%
Any Adverse Event	316	(88%)
Nausea	79	(22.0%)
Vomiting	78	(21.7%)
Malignant neoplasm progression	71	(19.8%)
Constipation	45	(12.5%)
Edema peripheral	43	(12.0%)
Somnolence	41	(11.4%)
Dyspnea	38	(10.6%)
Pyrexia	37	(10.3%)
Diarrhea	36	(10.0%)
Asthenia	35	(9.7%)
Fatigue	33	(9.2%)
Dizziness	29	(8.1%)
Application site irritation	23	(6.4%)
Cancer pain	22	(6.1%)
Anxiety	21	(5.8%)
Anemia	20	(5.6%)
Back pain	20	(5.6%)
Confusional state	20	(5.6%)
Headache	20	(5.6%)
Cough	19	(5.3%)
Insomnia	19	(5.3%)
Stomatitis	18	(5.0%)
Anorexia	17	(4.7%)
Dehydration	16	(4.5%)
Urinary tract infection	16	(4.5%)
Depression	13	(3.6%)
Oral candidiasis	13	(3.6%)
Abdominal pain	12	(3.3%)
Pain in extremity	12	(3.3%)
Arthralgia	11	(3.1%)
Decreased appetite	11	(3.1%)
Dry mouth	10	(2.8%)
Hallucination	10	(2.8%)
Hyperhidrosis	10	(2.8%)
Muscular weakness	10	(2.8%)
Pneumonia	10	(2.8%)
Pruritus	10	(2.8%)
Sedation	10	(2.8%)
Dysphagia	9	(2.5%)
Hypertension	9	(2.5%)
Increased bronchial secretion	9	(2.5%)
Lethargy	9	(2.5%)
Restlessness	9	(2.5%)
Tachycardia	9	(2.5%)
Bronchitis	8	(2.2%)

Appendix 1, continued

Dysuria	8	(2.2%)
Gastritis	8	(2.2%)
Hypokalemia	8	(2.2%)
Hyponatremia	8	(2.2%)
Neuralgia	8	(2.2%)
Abdominal distension	7	(1.9%)
Abdominal pain upper	7	(1.9%)
Agitation	7	(1.9%)
Cellulitis	7	(1.9%)
Deep vein thrombosis	7	(1.9%)
Disease progression	7	(1.9%)
Dyspnea exceptional	7	(1.9%)
Fall	7	(1.9%)
Hypoesthesia	7	(1.9%)
Neutropenia	7	(1.9%)
Pharyngolaryngeal pain	7	(1.9%)
Tremor	7	(1.9%)
Urinary retention	7	(1.9%)
Weight decreased	7	(1.9%)
Ascites	6	(1.7%)
Hypotension	6	(1.7%)
Productive cough	6	(1.7%)
Rash erythematous	6	(1.7%)
Blood glucose increased	5	(1.4%)
Chills	5	(1.4%)
Decubitus ULCER	5	(1.4%)
Disorientation	5	(1.4%)
Dysgeusia	5	(1.4%)
Dyspepsia	5	(1.4%)
Flatulence	5	(1.4%)
Leukopenia	5	(1.4%)
Lymphadenopathy	5	(1.4%)
Malaise	5	(1.4%)
Musculoskeletal pain	5	(1.4%)
Oral herpes	5	(1.4%)
Thrombocytopenia	5	(1.4%)
Vision blurred	5	(1.4%)
Wheezing	5	(1.4%)
Abdominal pain lower	4	(1.1%)
Blood alkaline phosphatase increased	4	(1.1%)
Blood lactate dehydrogenase increased	4	(1.1%)
Chest pain	4	(1.1%)
Contusion	4	(1.1%)
Drug withdrawal syndrome	4	(1.1%)
Dysphonia	4	(1.1%)
Gastroenteritis viral	4	(1.1%)
Gastroesophageal reflux disease	4	(1.1%)
Hiccups	4	(1.1%)
Influenza like illness	4	(1.1%)

Appendix 1, continued

Non-small cell lung cancer	4	(1.1%)
Odynophagia	4	(1.1%)
Pulmonary embolism	4	(1.1%)
Upper respiratory tract infection	4	(1.1%)
Urinary incontinence	4	(1.1%)
Viral infection	4	(1.1%)
Alopecia	3	(0.8%)
Amnesia	3	(0.8%)
Aspartate aminotransferase increased	3	(0.8%)
Blood bilirubin increased	3	(0.8%)
Blood creatinine increased	3	(0.8%)
Bone pain	3	(0.8%)
Cachexia	3	(0.8%)
Convulsion	3	(0.8%)
Ecchymosis	3	(0.8%)
Epistaxis	3	(0.8%)
Erythema	3	(0.8%)
Euphoric mood	3	(0.8%)
Gastroenteritis	3	(0.8%)
General physical health deterioration	3	(0.8%)
Generalised edema	3	(0.8%)
Hematemesis	3	(0.8%)
Hemoptysis	3	(0.8%)
Hot flush	3	(0.8%)
Hyperkalemia	3	(0.8%)
Hypoalbuminemia	3	(0.8%)
Hypocalcaemia	3	(0.8%)
Hypoproteinemia	3	(0.8%)
Hypoxia	3	(0.8%)
Irritability	3	(0.8%)
Joint swelling	3	(0.8%)
Laryngitis	3	(0.8%)
Localized edema	3	(0.8%)
Lymphedema	3	(0.8%)
Muscle spasms	3	(0.8%)
Myalgia	3	(0.8%)
Nasopharyngitis	3	(0.8%)
Neuropathy peripheral	3	(0.8%)
Neutropenic colitis	3	(0.8%)
Oral pain	3	(0.8%)
Pain	3	(0.8%)
Pancytopenia	3	(0.8%)
Pleural effusion	3	(0.8%)
Post procedural complication	3	(0.8%)
Procedural pain	3	(0.8%)
Prostate cancer	3	(0.8%)
Pulmonary congestion	3	(0.8%)
Renal failure acute	3	(0.8%)
Respiratory distress	3	(0.8%)
Rhonchi	3	(0.8%)

Appendix 1, continued

Sinus tachycardia	3	(0.8%)
Sinusitis	3	(0.8%)
Skin lesion	3	(0.8%)
Tooth fracture	3	(0.8%)
Vertigo	3	(0.8%)
Abdominal discomfort	2	(0.6%)
Abscess	2	(0.6%)
Acute respiratory distress syndrome	2	(0.6%)
Aphasia	2	(0.6%)
Aphthous stomatitis	2	(0.6%)
Application site anesthesia	2	(0.6%)
Areflexia	2	(0.6%)
Arrhythmia	2	(0.6%)
Ataxia	2	(0.6%)
Atelectasis	2	(0.6%)
Atrial fibrillation	2	(0.6%)
Bladder spasm	2	(0.6%)
Blister	2	(0.6%)
Blood potassium decreased	2	(0.6%)
Blood potassium increased	2	(0.6%)
Blood urea increased	2	(0.6%)
Breath sounds abnormal	2	(0.6%)
Cardiac failure congestive	2	(0.6%)
Chest discomfort	2	(0.6%)
Chronic obstructive pulmonary disease	2	(0.6%)
Disease	2	(0.6%)
Cold sweat	2	(0.6%)
Drug hypersensitivity	2	(0.6%)
Dry skin	2	(0.6%)
Electrolyte imbalance	2	(0.6%)
Excoriation	2	(0.6%)
Facial palsy	2	(0.6%)
Feeling drunk	2	(0.6%)
Fistula	2	(0.6%)
Flank pain	2	(0.6%)
Flushing	2	(0.6%)
Gastrointestinal motility disorder	2	(0.6%)
Glossitis	2	(0.6%)
Hematochezia	2	(0.6%)
Hematoma	2	(0.6%)
Hematuria	2	(0.6%)
Hemoglobin decreased	2	(0.6%)
Hepatic enzyme increased	2	(0.6%)
Hydronephrosis	2	(0.6%)
Hypomagnesaemia	2	(0.6%)
Hypopnea	2	(0.6%)
Influenza	2	(0.6%)
Jaundice	2	(0.6%)
Local swelling	2	(0.6%)

Appendix 1, continued

Lung cancer metastatic	2	(0.6%)
Malnutrition	2	(0.6%)
Mental status changes	2	(0.6%)
Metastases to bone	2	(0.6%)
Metastases to liver	2	(0.6%)
Mobility decreased	2	(0.6%)
Mucosal inflammation	2	(0.6%)
Nasal congestion	2	(0.6%)
Neck pain	2	(0.6%)
Nephrolithiasis	2	(0.6%)
Nervousness	2	(0.6%)
Neutrophil count decreased	2	(0.6%)
Night sweats	2	(0.6%)
Esophageal candidiasis	2	(0.6%)
Oral fungal infection	2	(0.6%)
Oral mucosal discoloration	2	(0.6%)
Panic attack	2	(0.6%)
Paraesthesia	2	(0.6%)
Paraesthesia oral	2	(0.6%)
Peroneal nerve palsy	2	(0.6%)
Pharmaceutical product complaint	2	(0.6%)
Pharyngitis	2	(0.6%)
Pneumonia aspiration	2	(0.6%)
Rash macular	2	(0.6%)
Rash pruritic	2	(0.6%)
Rectal hemorrhage	2	(0.6%)
Retching	2	(0.6%)
Rhinorrhea	2	(0.6%)
Sepsis syndrome	2	(0.6%)
Sinus bradycardia	2	(0.6%)
Skin atrophy	2	(0.6%)
Skin laceration	2	(0.6%)
Speech disorder	2	(0.6%)
Stasis dermatitis	2	(0.6%)
Supraventricular tachycardia	2	(0.6%)
Throat irritation	2	(0.6%)
Unresponsive to stimuli	2	(0.6%)
Vaginal hemorrhage	2	(0.6%)
Visual disturbance	2	(0.6%)
Wound infection	2	(0.6%)
Abasia	1	(0.3%)
Abdominal mass	1	(0.3%)
Abdominal tenderness	1	(0.3%)
Activated partial thromboplastin time prolonged	1	(0.3%)
Adverse drug reaction	1	(0.3%)
Alanine aminotransferase increased	1	(0.3%)
Allergy to metals	1	(0.3%)
Amenorrhea	1	(0.3%)
Apnea	1	(0.3%)

Appendix 1, continued

Application site dryness	1	(0.3%)
Arterial disorder	1	(0.3%)
Arthritis	1	(0.3%)
Asthma	1	(0.3%)
Back injury	1	(0.3%)
Bacteremia	1	(0.3%)
Bacterial sepsis	1	(0.3%)
Balance disorder	1	(0.3%)
Bladder cancer	1	(0.3%)
Bladder distension	1	(0.3%)
Blood chloride increased	1	(0.3%)
Blood cortisol decreased	1	(0.3%)
Blood electrolytes decreased	1	(0.3%)
Blood sodium increased	1	(0.3%)
Bradycardia	1	(0.3%)
Breast cancer metastatic	1	(0.3%)
Breast infection	1	(0.3%)
Breast pain	1	(0.3%)
Breast swelling	1	(0.3%)
Bronchitis viral	1	(0.3%)
Candidiasis	1	(0.3%)
Cardiac failure	1	(0.3%)
Cardiac murmur	1	(0.3%)
Cardio-respiratory arrest	1	(0.3%)
Cardiopulmonary failure	1	(0.3%)
Catheter related complication	1	(0.3%)
Catheter related infection	1	(0.3%)
Catheter site infection	1	(0.3%)
Cerebrovascular accident	1	(0.3%)
Cheilitis	1	(0.3%)
Cognitive disorder	1	(0.3%)
Colitis	1	(0.3%)
Colon cancer metastatic	1	(0.3%)
Concussion	1	(0.3%)
Conjunctival hyperemia	1	(0.3%)
CSF pressure increased	1	(0.3%)
Cystitis	1	(0.3%)
Deficiency anemia	1	(0.3%)
Depressed level of consciousness	1	(0.3%)
Dermatitis contact	1	(0.3%)
Device breakage	1	(0.3%)
Diarrhea infectious	1	(0.3%)
Disturbance in attention	1	(0.3%)
Diverticulitis	1	(0.3%)
Dry eye	1	(0.3%)
Dyskinesia	1	(0.3%)
Dyspnea paroxysmal nocturnal	1	(0.3%)
Ear discomfort	1	(0.3%)
Ear infection	1	(0.3%)
Ear pain	1	(0.3%)
Electrocardiogram abnormal	1	(0.3%)

Appendix 1, continued

Electrocardiogram QRS complex abnormal	1	(0.3%)
Electrocardiogram QT prolonged	1	(0.3%)
Emphysema	1	(0.3%)
Enteritis	1	(0.3%)
Enteritis infectious	1	(0.3%)
Eosinophilia	1	(0.3%)
Epicondylitis	1	(0.3%)
Epididymitis	1	(0.3%)
Erectile dysfunction	1	(0.3%)
Extradural abscess	1	(0.3%)
Eyelid edema	1	(0.3%)
Facial wasting	1	(0.3%)
Fecaloma	1	(0.3%)
Febrile neutropenia	1	(0.3%)
Feeling abnormal	1	(0.3%)
Femoral neck fracture	1	(0.3%)
Fibula fracture	1	(0.3%)
Filariasis	1	(0.3%)
Food poisoning	1	(0.3%)
Fundoscopy abnormal	1	(0.3%)
Fungal infection	1	(0.3%)
Fungus sputum test positive	1	(0.3%)
Furuncle	1	(0.3%)
Gait disturbance	1	(0.3%)
Gastric ulcer	1	(0.3%)
Gastrointestinal disorder	1	(0.3%)
Gastrointestinal fistula	1	(0.3%)
Gastrointestinal hemorrhage	1	(0.3%)
Gastrointestinal sounds abnormal	1	(0.3%)
Genital discharge	1	(0.3%)
Genital swelling	1	(0.3%)
Gingival bleeding	1	(0.3%)
Gingival discoloration	1	(0.3%)
Gingival hyperplasia	1	(0.3%)
Gingival edema	1	(0.3%)
Glossodynia	1	(0.3%)
Glucose tolerance impaired	1	(0.3%)
Hemorrhage intracranial	1	(0.3%)
Herpes zoster	1	(0.3%)
Hip fracture	1	(0.3%)
Humerus fracture	1	(0.3%)
Hydrocephalus	1	(0.3%)
Hyperbilirubinemia	1	(0.3%)
Hypercalcemia	1	(0.3%)
Hypercapnia	1	(0.3%)
Hyperchlorhydria	1	(0.3%)
Hyperglycemia	1	(0.3%)
Hyperkeratosis	1	(0.3%)
Hyperreflexia	1	(0.3%)
Hypoesthesia oral	1	(0.3%)
Hypogeusia	1	(0.3%)

Appendix 1, continued

Hypoglycemia	1	(0.3%)
Hypokinesia	1	(0.3%)
Hypophosphatemia	1	(0.3%)
Hypothyroidism	1	(0.3%)
Implant site pain	1	(0.3%)
Incision site infection	1	(0.3%)
Increased appetite	1	(0.3%)
Increased upper airway secretion	1	(0.3%)
Increased viscosity of bronchial secretion	1	(0.3%)
Induration	1	(0.3%)
Infection	1	(0.3%)
Injury corneal	1	(0.3%)
Intention tremor	1	(0.3%)
International normalized ratio decreased	1	(0.3%)
Jaundice cholestatic	1	(0.3%)
Joint sprain	1	(0.3%)
Kidney infection	1	(0.3%)
Kyphosis	1	(0.3%)
Laryngeal cancer	1	(0.3%)
Leukocytosis	1	(0.3%)
Limb discomfort	1	(0.3%)
Limb injury	1	(0.3%)
Lip and/or oral cavity cancer	1	(0.3%)
Lip disorder	1	(0.3%)
Lip hemorrhage	1	(0.3%)
Lip ulceration	1	(0.3%)
Liver abscess	1	(0.3%)
Lobar pneumonia	1	(0.3%)
Localized intraabdominal fluid collection	1	(0.3%)
Loss of consciousness	1	(0.3%)
Lower respiratory tract infection	1	(0.3%)
Lung neoplasm malignant	1	(0.3%)
Lymphangitis	1	(0.3%)
Lymphocyte count decreased	1	(0.3%)
Lymphocyte count increased	1	(0.3%)
Lymphopenia	1	(0.3%)
Malignant ascites	1	(0.3%)
Mass	1	(0.3%)
Medical device complication	1	(0.3%)
Melena	1	(0.3%)
Metabolic acidosis	1	(0.3%)
Metastases to central nervous system	1	(0.3%)
Metastases to pleura	1	(0.3%)
Metastases to skin	1	(0.3%)
Metastases to spine	1	(0.3%)
Metastatic neoplasm	1	(0.3%)
Micturition urgency	1	(0.3%)
Migraine	1	(0.3%)

Appendix 1, continued

Monocyte count increased	1	(0.3%)
Monoparesis	1	(0.3%)
Mood swings	1	(0.3%)
Multiple myeloma	1	(0.3%)
Muscle atrophy	1	(0.3%)
Musculoskeletal chest pain	1	(0.3%)
Myelodysplastic syndrome	1	(0.3%)
Myocardial infarction	1	(0.3%)
Myositis	1	(0.3%)
Neoplasm	1	(0.3%)
Neurogenic bladder	1	(0.3%)
Neutrophil count increased	1	(0.3%)
Nightmare	1	(0.3%)
Edema mouth	1	(0.3%)
Esophageal stenosis	1	(0.3%)
Open wound	1	(0.3%)
Optic discs blurred	1	(0.3%)
Oral disorder	1	(0.3%)
Oral intake reduced	1	(0.3%)
Oral mucosal blistering	1	(0.3%)
Oral neoplasm	1	(0.3%)
Oral viral infection	1	(0.3%)
Orthopnea	1	(0.3%)
Orthostatic hypotension	1	(0.3%)
Osteoarthritis	1	(0.3%)
Otorrhoea	1	(0.3%)
Palmar-plantar erythrodysesthesia syndrome	1	(0.3%)
Paranoia	1	(0.3%)
Paraparesis	1	(0.3%)
Paraplegia	1	(0.3%)
Periodontal disease	1	(0.3%)
Periorbital edema	1	(0.3%)
Peripheral coldness	1	(0.3%)
Pharyngeal candidiasis	1	(0.3%)
Pharyngeal erythema	1	(0.3%)
Pharyngeal inflammation	1	(0.3%)
Physical examination abnormal	1	(0.3%)
Pitting edema	1	(0.3%)
Platelet count decreased	1	(0.3%)
Platelet count increased	1	(0.3%)
Pneumonitis	1	(0.3%)
Pollakiuria	1	(0.3%)
Polycythaemia vera	1	(0.3%)
Polydipsia	1	(0.3%)
Post-traumatic pain	1	(0.3%)
Postnasal drip	1	(0.3%)
Proctalgia	1	(0.3%)
Prothrombin time prolonged	1	(0.3%)
Pruritus generalized	1	(0.3%)
Purulent discharge	1	(0.3%)
Pyelonephritis	1	(0.3%)

Appendix 1, continued

Pyloric stenosis	1	(0.3%)
Radiation injury	1	(0.3%)
Radiation mucositis	1	(0.3%)
Radiation skin injury	1	(0.3%)
Rales	1	(0.3%)
Rash	1	(0.3%)
Rash maculo-papular	1	(0.3%)
Rash papular	1	(0.3%)
Recurrent cancer	1	(0.3%)
Renal cyst	1	(0.3%)
Renal failure chronic	1	(0.3%)
Renal impairment	1	(0.3%)
Respiratory depression	1	(0.3%)
Respiratory failure	1	(0.3%)
Respiratory tract congestion	1	(0.3%)
Restless legs syndrome	1	(0.3%)
Retinopathy	1	(0.3%)
Reversible posterior leukoencephalopathy syndrome	1	(0.3%)
Rib fracture	1	(0.3%)
Right ventricular hypertrophy	1	(0.3%)
Salivary gland enlargement	1	(0.3%)
Sarcopenia	1	(0.3%)
Scar	1	(0.3%)
Scrotal edema	1	(0.3%)
Sensitivity of teeth	1	(0.3%)
Sepsis	1	(0.3%)
Septic shock	1	(0.3%)
Sinus arrhythmia	1	(0.3%)
Skin discoloration	1	(0.3%)
Skin exfoliation	1	(0.3%)
Skin fissures	1	(0.3%)
Skin inflammation	1	(0.3%)
Skin injury	1	(0.3%)
Skin ulcer	1	(0.3%)
Spinal cord disorder	1	(0.3%)
Spinal cord neoplasm	1	(0.3%)
Streptococcal bacteremia	1	(0.3%)
Suicidal ideation	1	(0.3%)
Sunburn	1	(0.3%)
Swelling face	1	(0.3%)
Syncope vasovagal	1	(0.3%)
Tachypnea	1	(0.3%)
Tendon pain	1	(0.3%)
Thirst	1	(0.3%)
Thrombocythemia	1	(0.3%)
Thrombophlebitis	1	(0.3%)
Tongue coated	1	(0.3%)
Tongue disorder	1	(0.3%)
Tongue dry	1	(0.3%)
Tongue injury	1	(0.3%)
Tongue edema	1	(0.3%)

Appendix 1, continued

Tongue ulceration	1	(0.3%)
Tonsillar disorder	1	(0.3%)
Tonsillar hemorrhage	1	(0.3%)
Tooth erosion	1	(0.3%)
Tooth infection	1	(0.3%)
Typhoid fever	1	(0.3%)
Urethral stenosis	1	(0.3%)
Urinary retention postoperative	1	(0.3%)
Urinary tract infection enterococcal	1	(0.3%)
Urinary tract pain	1	(0.3%)
Urine osmolality increased	1	(0.3%)
Urostomy complication	1	(0.3%)
Urticaria	1	(0.3%)
Vaginal infection	1	(0.3%)
Vaginal ulceration	1	(0.3%)
Venous stasis	1	(0.3%)
Viral upper respiratory tract infection	1	(0.3%)
Visual acuity reduced	1	(0.3%)
Waist circumference increased	1	(0.3%)
Weight increased	1	(0.3%)
White blood cell count increased	1	(0.3%)
Wound	1	(0.3%)

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/s/

SHARON H HERTZ
12/28/2011