CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-338

MEDICAL REVIEW(S)

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	May 22, 2006
DRUG:	IONSYS (fentanyl iontophoretic transdermal system) 40 mcg/activation, Patient-activated
NDA:	21-338
SPONSOR:	ALZA Corporation
INDICATION:	indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization

ALZA Corporation submitted this NDA for IONSYS (fentanyl iontophoretic transdermal system) 40 mcg/activation, Patient-activated, on September 23, 2004. An approvable letter was issued on July 23, 2004. This response to the approvable letter was received on November 22, 2005. IONSYS is a transdermal iontophoretic delivery system that provides 40 mcg of fentanyl per patient activation, after an initial ramp-up period. It is indicated only for the treatment of post-operative pain during hospitalization and must be removed by a health care practitioner prior to the patient being discharged. Patients must be titrated to comfort with IV analgesics prior to treatment with IONSYS, and have rescue medication available during IONSYS treatment, particularly during the initial dosing ramp-up period. Please see my approvable memo dated June 23, 2004 for additional details on the product.

The outstanding concerns raised in the approvable letter are summarized below:

- The data submitted in the application were insufficient to assure the safe use of the Patient and Health-Care Provider product instructions and product performance testing.

- The data submitted in the application were insufficient to assure the safe conversion from and adjunctive therapy with other opioid analgesics during the early treatment phase with IONSYS.

- Impurities containing — that are structural alerts for mutagenicity needed to be reduced in the drug substance or qualified in appropriate genotoxicology studies.

- The — impurity in the drug substance needed to be reduced.

- Certain drug product specifications required revision.

- The drug product stability was insufficient to allow the requested expiration dating.

- A revision to the post-approval stability commitment was needed.

- Revisions to the comparability protocols were necessary.

- Changes to the product package insert, and system and immediate carton and container labels were necessary.

In addition, the sponsor was reminded that they must address the issues related to the safe manufacturing of the device that had been described in the CDRH Discipline Review Letter, and that they needed to finalize an adequate Risk Management Plan for the product.

The clinical studies in this resubmission were reviewed by Lex Schultheis, M.D., Ph.D. The CMC data was reviewed by Rajiv Agarwal, Ph.D. The pharmacology/toxicology portion of the submission was reviewed by Mamata De, Ph.D. Consultations on this application were provided by the Office of Surveillance and Epidemiology (OSE), the Controlled Substances Staff, the Center for Devices and Radiological Health (CDRH), and the Division of Drug Marketing, Advertising and Communications. In particular, the sponsor submitted ' — ' that was reviewed by the Division of Surveillance, Research and Communication Support in OSE, and they have found it to be acceptable, but with a new title, "Patient Bedside Information Sheet." The outstanding toxicological, manufacturing and control issues have been adequately addressed in this resubmission as documented in the reviews completed by Drs. Agarwal and De. The sponsor has also adequately addressed the concerns regarding the safe manufacturing of the device raised by CDRH. The sponsor has agreed to all changes to the product package insert, and carton and container labeling requested by the Division.

During the first cycle review, the Division noted that there were a high number of product failures. The sponsor modified some design features and found that a large

number of the product failures were due to [redacted]. The sponsor reported that this problem had been rectified and the system quality does appear to be somewhat improved based upon the results of the new studies. The product labeling also now requires functionality testing by the pharmacist or pharmacy technician prior to removal from the packaging. A system for returning failed units to the distributor has been addressed in the package insert.

The sponsor submitted three new, open-label studies which examined the use of IONSYS by patients and health care practitioners. In addition, they submitted the results of a survey of nurses who had been responsible for administering, monitoring and removing the device from patients during the first two studies. Dr. Schultheis has reviewed the results of the studies in detail and he has concluded that the sponsor has provided documentation that the instructions for use and product performance testing are adequate to allow the safe use of the product in hospitalized post-operative patients. He also reviewed the results of the sponsor's Nursing Survey and found that it indicated that, for the vast majority of nurses, proper use of the product was not particularly difficult or onerous, particularly after the nurses had treated, on average, ten patients.

The three studies, CAPSS-319, CAPSS-320 and FEN-PPA-401, exposed 972 patients to treatment with IONSYS, and included a comparator arm that exposed patients to treatment with IV patient-controlled analgesia with morphine. Controlled studies were not requested by the Division and these studies were inadequately designed to support any conclusions regarding comparisons of IONSYS to the control. Therefore, I will not address the results of the control groups in this memo, other than to note that the incidence of adverse events was similar between the two treatment groups with one exception. This exception was the increased incidence of skin reactions noted with IONSYS. These reactions were not serious and resolved after treatment in all cases. It is important to note that there was no increase in adverse events during the initial hours of treatment with IONSYS compared to treatment after full doses were expected to have been delivered from the system. This supports the sponsor's contention that there are no safety concerns related to conversion from IV analgesic treatment to treatment with IONSYS, or related to the use of rescue analgesia during the initial IONSYS-treatment period. The salient evaluation included in these studies was the "Summary of Nurse Ease-of-Care Questionnaire at Last Assessment" that queried the nurses regarding overall ease of use, how bothersome they found using the system, how time-consuming they found using the system, and satisfaction with use.

In his review, Dr. Schultheis has expressed the opinion that, "Significant clinical feasibility concerns related to nursing instructions for product use and disposal became apparent during this review [sic] may need resolution before IONSYS may be safely introduced into general use." His concern was primarily focused on the fact that the results of the studies included data from research and study-coordinator nurses, in addition to the staff nurses responsible for the day-to-day care of the subjects, and that the staff nurses had significantly less success in using the system than did the research or

study-coordinator nurses. While I do think the data from the research and study-coordinator nurses is less useful than that obtained from the staff nurses, I do not think that this is a defining flaw in the sponsor's response. Indeed, when the sponsor reanalyzed the data at the Divison's request, using only the data from the staff nurses, the results still demonstrated a robust finding that the IONSYS system can be used without significant difficulty. The results of that reanalysis are documented in the table attached to this memo as Appendix 1, reproduced from the sponsor's communication, dated May 18, 2006.

The Nursing Survey, conducted after the conclusion of the two CAPSS studies, was undertaken to assess nurse comprehension of the educational materials. Of the responding nurses, 90% indicated that they felt comfortable using IONSYS. These data were obtained from the research and study-coordinator nurses in addition to the staff nurses. When the data from the staff nurses were analyzed separately, only 63% of the nurses were able to correctly answer that a dose was being delivered when the light was continuously lit. However, this percentage increased to 94% for those staff nurses who had provided care for more than ten patients treated with IONSYS. Similar results were found for the responses to the "correct identification of the administered dose" query in the survey. Results from the studies were also supportive in that ease of use appeared to increase after the nurses had treated nine patients.

While the sponsor has made a good faith effort to improve the Risk Management Plan for IONSYS, there are still a number of outstanding deficiencies and changes that need to be addressed, based on ongoing discussions between the sponsor and the Division, the OSE staff and the Controlled Substances Staff.

During the first review cycle, the Division raised a concern regarding appropriate disposal of the IONSYS system. Even after administration of the maximum number of doses, over 6 mg of fentanyl remain in the housing. The fentanyl is formulated in a gel that cannot easily be disposed of by dissolution. As this quantity of fentanyl poses a significant risk for diversion, it is essential that a safe method of disposal be defined for the product. After numerous discussions between the sponsor, the OSE staff, the Controlled Substances Staff, and the Division, we have reached consensus that, after removal, folding the system over itself to enclose the remaining fentanyl, while assuring that the edges are adherent to each other, and then flushing the system down the toilet, is the optimal available method for disposal.

The initial approvable letter did not address the use of IONSYS

The sponsor has agreed to limit the distribution of the product to hospitals. As noted above, a system for returning failed units to the distributor has been addressed in the package insert.

Discussion:

The sponsor has adequately addressed the concerns raised in the approvable letter in their response and during follow-up discussions with the Division. IONSYS will only be distributed for use in hospitalized patients under the supervision of health care professionals. The in-use studies and Nursing Survey have documented that there are no outstanding safety concerns and that the use of the product by patients and professional staff is neither overly difficult nor onerous, when the approved instructions for use and labeling are adhered to. It appears that the use of the product becomes more acceptable to nurses after they have overseen use in nine to ten patients. This finding is not an unusual nor unexpected one for a novel medical treatment. A reasonable system for disposal has been agreed upon, and the return of failed systems has been addressed in the package insert. All product quality and manufacturing and controls concerns have been appropriately responded to and resolved.

The remaining concern related to the distribution and use of IONSYS is that it is likely to be the target of abuse and diversion. Fentanyl is a highly sought after drug of abuse, and the IONSYS housing will contain large quantities of fentanyl even after the maximum number of doses has been administered. Abuse by health care practitioners is of particular concern with this product. The current iteration of the sponsor's Risk Management Plan will require further improvements before it can adequately address the abuse liability, as well as the potential for misuse of IONSYS.

Action: Approval

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

Appendix 1

TABLE 1								
Summary of Ease of Care Responses on IONSYS Use by STAFF NURSES in CAPSS 319, 320, & FEN-401 Combined								
(All reponses of "NOT RESPONSIBLE" for a particular IONSYS function were excluded from this analysis)								
ETRANS		Staff Nurse Responders (N)	Not at all	A little bit	Somewhat	Quite a bit	A great deal	A very great deal
Time Consuming								
1	Accessing device-related supplies	185	41.6%	38.4%	12.4%	3.8%	2.2%	1.6%
2	Initial set up of device	111	45.0%	37.8%	11.7%	3.6%	0.0%	1.8%
3	Maintaining device function	334	57.2%	26.6%	11.1%	2.4%	1.5%	1.2%
4	Changing or adjusting the device due to malfunction or dosing schedule	201	56.7%	24.9%	11.4%	3.5%	3.0%	0.5%
5	Educating/re-instructing patient on how to use device	466	37.8%	39.7%	15.2%	5.2%	1.1%	1.1%
6	Positioning, moving, or transferrring the patient with the device	532	76.1%	15.4%	4.3%	1.9%	1.1%	1.1%
7	Managing breakthrough pain	500	44.6%	33.4%	14.0%	5.0%	2.2%	0.8%
8	Treating patient problems related to the device (dosing, skin irritation, infiltration, etc.)	459	61.9%	25.7%	8.3%	3.1%	0.7%	0.4%
9	Determining amount of medication provided to patient	373	37.5%	38.3%	15.8%	4.0%	2.1%	2.1%
10	Removing or disposing of device, including medication	253	54.9%	36.8%	5.1%	1.2%	0.8%	1.2%
How Bothersome								
11	Accessing device-related supplies	188	60.1%	26.1%	9.0%	2.1%	1.1%	1.6%
12	Initial set up of device	109	67.0%	20.2%	6.4%	4.6%	0.9%	0.9%
13	Maintaining device function	336	67.0%	24.7%	6.3%	1.2%	0.6%	0.3%
14	Changing or adjusting the device due to malfunction or dosing schedule	209	63.6%	21.5%	10.0%	2.9%	1.0%	1.0%
15	Educating/re-instructing patient on how to use device	476	64.9%	22.3%	8.0%	3.4%	1.1%	0.4%
16	Positioning, moving, or transferrring the patient with the device	537	83.6%	9.9%	3.4%	1.7%	0.7%	0.7%
17	Managing breakthrough pain	504	58.3%	26.0%	9.5%	3.6%	1.4%	1.2%
18	Treating patient problems related to the device (dosing, skin irritation, infiltration, etc.)	451	70.3%	21.5%	4.9%	2.9%	0.0%	0.4%
19	Determining amount of medication provided to patient	380	53.2%	26.1%	12.4%	5.3%	1.6%	1.6%
20	Removing or disposing of device, including medication	255	72.5%	21.6%	2.7%	1.6%	0.0%	1.6%

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/s/

Bob Rappaport
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MEDICAL OFFICER

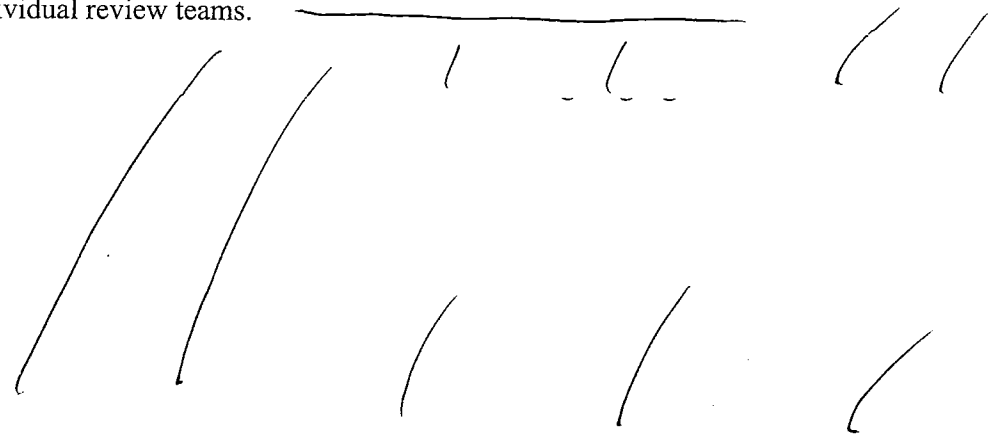
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Addendum To Clinical Review: Comments on Consultants' Responses

NDA#:	21-338
Drug Name (generic):	IONSYS™ (fentanyl iontophoretic transdermal system)
Sponsor:	Alza Corporation
Indication:	short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization.
Type of Submission:	Secondary NDA Review
Reviewer:	Lex Schultheis, M.D., Ph.D. (DAARP)

1. Office of Drug Safety: Division of Medication Errors and Technical Support: Consultant's response, March 8, 2006

- Point-by-point consideration of the suggestions offered in the consult were reviewed in the Division labeling review meetings of 5/1, 5/8, 5/11, 5/15, 5/18 and 5/19 and by the individual review teams.



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/s/

Lester Schultheis
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5/22/2006 05:55:44 PM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-338
Submission Code	AZ
Letter Date	November 21, 2005
Stamp Date	November 22, 2005
PDUFA Goal Date	May 22, 2006
Reviewer Name	Lex Schultheis, M.D., Ph.D.
Project Manager	Kim Compton, R.Ph.
Review Completion Date	April 26, 2006
Established Name	Fentanyl HCl
(Proposed) Trade Name	IONSYS™ (Fentanyl HCl Patient-Activated Transdermal System)
Therapeutic Class	Analgesic
Applicant	ALZA (Johnson & Johnson)

Priority Designation S

Formulation Self-contained system for patient-controlled iontophoretic transdermal administration of fentanyl in hydrogel.

Dosing Regimen: 40-mcg (44 mcg fentanyl HCl) dose of fentanyl over a 10-minute period upon each activation

Indication: short-term, acute postoperative pain in hospitalized adult surgical patients requiring opioids

Intended Population: hospitalized adult surgical patients requiring opioids

Table of Contents

1 EXECUTIVE SUMMARY

ALZA, Corp. has submitted NDA 21-338 for a second cycle review in support of marketing approval for IONSYS, their patient-controlled, transdermal, iontophoretic delivery system for fentanyl HCl. This drug-device combination product delivers 40 mcg of fentanyl HCl iontophetically over 10 minutes when activated, and incorporates a 10-minute lockout period between allowed activations. After a maximum of 80 doses, or after 24 hours, the device can no longer be activated. The device is composed of two layers. The top layer contains a 3-volt lithium battery and other electronic components. The bottom layer contains the skin adhesive and two hydrogel reservoirs, an anode containing 10,800 mcg of fentanyl HCl and a cathode containing pharmacologically inactive materials. The IONSYS system has been developed for use in medically supervised settings by patients requiring short-duration analgesia for acute perioperative pain.

1.1 Recommendation on Regulatory Action

IONSYS is recommended for an approvable action pending resolution of outstanding clinical feasibility concerns.

The following evidence supports an approval action:

- Efficacy for the indication treatment of postoperative pain was demonstrated by analysis of data from adequate and well controlled clinical trials C-95-016 (016), C-2000-008 (008) and C-2001-011 (011). These three studies were single-application, randomized, placebo-controlled, double-blind, parallel-group trials comparing IONSYS (previously called E-TRANS) to placebo, performed in patients with acute post-operative pain previously reviewed July 23, 2004. Subjects were adults requiring at least 24 hours of opioid treatment post-operatively, who were to have been titrated to a comfortable level of pain control with IV opioids in the PACU. Subjects were then randomized to receive a single application of IONSYS or matching placebo for use during the first 24 hours post-operatively. IV fentanyl administration was permitted during the first three hours after study drug application. Subjects were considered to have completed the study after 24 hours from study drug application or after 80 doses had been delivered, whichever came first. The primary efficacy outcome was defined as the number of patients in each treatment group who dropped out of the study more than three hours after initiation of therapy due to inadequate pain control. The secondary outcome measures included: pain intensity, patient global assessment, investigator global assessment, number of on-demand doses delivered, number of patients requiring re-titration to comfort, and assessment of the adherence of IONSYS.

- Safety of patients treated with IONSYS has been supported by additional new open label active-controlled studies CAPSS 319, CAPSS 320 and FEN-PPA-401 included with the Sponsor's NDA reapplication of November 21, 2006. In these studies IONSYS was

compared in 972 patients to 993 patients using morphine IV Patient-Controlled Analgesia (PCA). In particular, the evidence for patient safety is based upon a comparable adverse event profile of IONSYS when compared to morphine IV PCA. Although the dose of rescue opioid in the first three hours of treatment was somewhat higher among IONSYS than IV PCA treatment groups, the differences were not clinically relevant and are not expected to complicate treatment or increase patient risk. These data appear to adequately resolve earlier concerns regarding the ability to convert from and provide adjunctive therapy with other opioid analgesics during the early treatment phase with IONSYS. Another concern that remained following the earlier review was that learning how to use IONSYS appeared difficult and the instructional material had not demonstrated that IONSYS could be used safely. The new studies included patient, nurse, pharmacist and physical therapist questionnaires that evaluated the feasibility of IONSYS in the hospital setting. Furthermore, an important safety feature of IONSYS is an automatic lockout system incorporated into the device that prevents administration of drug in excessive doses.

Significant clinical feasibility concerns related to nursing instructions for product use and disposal became apparent during this review may need resolution before IONSYS may be safely introduced into general use.

1. Research or study coordinator nurses as-well-as patient care nurses completed the nursing Ease-of-use questionnaire that the sponsor used to support the adequacy of instructional material to nurses. The frequent use of non-staff nurses to test instructional material is likely to have introduced bias into the Sponsor's analysis because research or study coordinator nurses are expected to be substantially familiar with the IONSYS system may be less familiar than the staff nurses with the IV PCA pumps available in each study site. Research and study coordinator nurses are not expected to rely exclusively on the IONSYS instructional material as heavily as did the patient care nurses.

Table 1.1-1 Summary Nursing Ease-of-Use Questionnaire: Completion Frequency by Staff, Research or Study Nurse

	Staff (Patient Care) Nurses		Research or Study Coordinator Nurses	
Study	IONSYS	IV PCA	IONSYS	IV PCA
CAPSS-319	249/349 (66%)	218/325(67%)	130/349 (44%)	107/325 (33%)
CAPSS-320	131/232 (57%)	120/221 (54%)	101/232 (43%)	101/221 (46%)
FEN-PPA-401	Nurses were not differentiated according to their primary responsibility			

Data are presented as the ratio (percentage) of the number of questionnaires completed according to work assignment to the total number of completed questionnaires. Data were abstracted from Sponsor's Tables 11.2.7-11A, B, C and D from Study Report CAPSS-319 pp. 424 through 31, Tables 11.2.7-5A, B, C and D from Study Report CAPSS-320 pp. 352 through 359, and Table 11.2.6.3-1 from Study Report FEN-PPA-401 page 182.

2. The nursing Ease-of-Use questionnaire data indicated that someone other than the nurse was frequently responsible for

- evaluating the number of doses delivered to the patient
- disposal of the unused drug product

in a higher proportion for IONSYS compared to IV PCA treatment arms for studies CAPSS 319, CAPSS 320 and FEN-PPA-401. Nurses are expected to be primarily responsible for determination of the number of doses delivered and disposal of unused drug in the actual practice setting. These findings may suggest that nurses found IONSYS more complicated than IV PCA when determining the number of doses delivered or disposing of residual drug and relied on other investigators to support these activities.

Table 1.1-2 Summary Nursing Ease-of-Use Questionnaire: Estimation of the Number of Delivered Doses and Disposal of the Product

Someone Other Than the Nurse Was Responsible for Product Evaluation in Studies 319, 320, 401		
	IONSYS N=840	IV PCA N=761
Estimation of Doses Delivered	n=233 (28%)	n=133(13%)
Disposal of Remaining Drug	n=382 (45%)	n=220 (29%)

The nursing Ease-of –Use Questionnaire was used to evaluate how time-consuming (questions 9 and 10) and bothersome (questions 19 and 20) the product was to use. Data were abstracted from Sponsor's Tables 11.2.7-15, 11.2.7-9 and 11.2.6.3-4 from Study reports 319, 320 and 401 respectively. "N" refers to total number of nurse questionnaires returned. "n" refers to the average of nurse questionnaires answered with a response that someone other than the nurse was responsible for the task of evaluating the number of doses delivered (questions 9 and 19) or disposal (questions 10 and 20) of the unused product. These data were not differentiated according to the primary responsibility of the nurse (staff vs. research or study coordinator).

This conclusion is supported by the finding of a higher frequency of missing responses to questions about how time consuming or bothersome IONSYS was compared to IV PCA for Studies CAPSS-319 and CAPSS-320.

3. In a post-study Nursing Survey following Studies CAPSS-319 or CAPSS-320, 90% of the nurses who had care for about ten patients were able to correctly answer questions about the dose of fentanyl delivered by IONSYS. The percentage of nurses giving correct answers decreased with among nurses with less experience with the product.

4. The Sponsor has not tested their suggested method (Risk Management Plan March 20, 2006) of disposal for unused drug product. The proposed method of disposal of unused drug by flushing down the toilet was accepted for Duragesic, a transdermal fentanyl product (NDA 19-813, August 7, 1990) indicated for management of chronic pain. However, the size and construction of IONSYS may not make this method of disposal practical. An earlier proposal (Risk Management Plan November 22, 2006) to

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor's clinical data in the current submission did not fully demonstrate the safe use of product instructional material for use in a typical clinical setting because of the following deficiencies:

1. The Sponsors's Risk Management Plan of March 20, 2006 indicated [redacted] On April 21, 2006 the Sponsor communicated their intention by email to restrict marketing of IONSYS for use by hospitals and associated inpatient pharmacies.

2. The Sponsor's Risk Management Plan as submitted November 22, 2005 indicated that the product was to be marketed t [redacted] and the Sponsor subsequently revised their Risk Management Plan (March 20, 2006) to include only specialists who manage patients with acute perioperative pain.

3. Significant concerns remain regarding the abuse liability of the IONSYS system and the adequacy of the sponsor's proposed Risk Management Plan (RMP). Fentanyl is a highly desirable drug of abuse, sought by substance abusers in and out of the health-care system. This product contains a total of 7600 mcg of fentanyl even after complete delivery of all allowable doses. The gel containing the fentanyl is easily removed from the device, and the fentanyl may then be extracted from the gel. A recent proposal (March 20, 2006) to dispose of residual IONSYS fentanyl by flushing the drug reservoir down a toilet may not be acceptable because the used product is folded over and sealed by its own adhesive, thereby protecting the fentanyl from dissolution. While flushing the IONSYS unit has not been tested, it is notable that the drug reservoir is a stiff plastic that does not degrade in water. Duragesic is an approved fentanyl reservoir product with flushing as the labeled method of disposal, but the reservoir is more deformable than that of IONSYS and Duragesic is indicated for home use where disposal options of controlled substances is more limited than in a hospital.

1.2.2 Required Phase 4 Commitments

Trials are required to demonstrate efficacy in post-surgical pediatric patients between 6 and 18 years old because the use of patient controlled analgesia has been reported in pediatric patients as young as 6 years of age.

1.3 Summary of Clinical Findings

Risk-Benefit Analysis

Risk
This review incorporated a risk to benefit analysis of IONSYS as compared to IV PCA, the comparator used by the Sponsor in clinical studies. IONSYS, by its design as a solid state transdermal system, eliminates certain fundamental IV PCA risks capable of causing severe clinical effects such as inadvertent administration of look-alike drugs, improper dilution of drug, incorrect programming of PCA pump, catheter attachment error, and pump flow-rate error.

However, the semisolid state design of IONSYS also introduces opportunities for novel adverse events including skin reactions, risk of exposure by health care personnel to concentrated fentanyl, a potentially confusing indicator of delivered doses and a unique problem of drug disposal. In particular, there is no precedent method among controlled drugs for disposal of a formulation similar to the fentanyl depot in the base of IONSYS. The Sponsor's past proposal to dispose of the drug containing component of IONSYS [redacted]. A suggestion to flush the drug containing component down the toilet in the Sponsor's RMP of March 20, 2006 has not been tested.

The incidence, seriousness, severity and nature of systemic adverse events appear similar between IONSYS and IV PCA. Topical toxicity is present only with IONSYS, as expected, because of its transdermal route of administration, but the skin reactions reported with its use were not serious.

Benefit
IONSYS was determined to be effective for the indication of post operative analgesia in the previous review cycle. A remaining concern was that that a period of three hours of access to rescue medication may be needed prior to reliance on the effectiveness of IONSYS. The basis for this concern was a high drop-out rate in study C-2000-008 during the first three hours of treatment with IONSYS that appeared to account for an inability to distinguish efficacy of IONSYS from placebo. This explanation was supported by pharmacokinetic findings that only 17 mcg of the nominal 40 mcg dose of fentanyl was absorbed at treatment initiation.

A delay in onset of efficacy could complicate dosing rescue opioids if the timing of onset of analgesia from IONSYS were unpredictable. Clinical study reports in the current submission contained an analysis of rescue opioid dosing in the early postoperative period comparing IONSYS to IV PCA treatment arms. In these studies, the total dose of rescue opioid in the first

three hours of use was higher among patients treated with IONSYS than IV PCA, but the difference in dosing was small and therefore not expected to change clinical outcomes or complicate treatment because it is coincident with the time patients are vigilantly monitored after surgery.

Conclusion

The overall risk-benefit evaluation of this review is primarily based upon the impact of this product on the health of the patients it is intended to treat. The overall effect that IONSYS may be anticipated to have on the health care system is also considered.

The health risk to post-surgical patients based upon adverse events associated with IONSYS is comparable to IV PCA in the hospital setting. The possibility that the product may not be used safely has not been fully resolved because review of the recently submitted clinical studies reveals that they do not represent the intended clinical practice environment. For example, analysis of the data from the nursing Ease-of-Use Questionnaire revealed a high level of participation by research nurses as opposed to patient care nurses in the IONSYS arms compared to the IV PCA arms. Furthermore, the study data indicated that someone other than the nurse completing the questionnaire had been responsible for important decisions regarding delivered dose and disposal more frequently in the IONSYS groups than in the IV PCA groups. Although the Ease-of-Use Questionare was not designed to assess the level of nursing knowledge regarding the use of the IONSYS system, it does suggest that there was a difference in practice between IONSYS and IV PCA. This difference may be explained by a tendency of patient care nurses to defer novel tasks to investigators during a research study.

A Nurse Survey conducted after the conclusion of two of the recently submitted active-controlled studies (CAPSS-319 and CAPSS-320) was the tool identified by the Sponsor intended to assess nurse comprehension of educational materials. Of the responding nurses, 90% indicated that they felt comfortable using IONSYS. However, among nurses that provided care for 1 to 3 patients treated with IONSYS only 63% were able to correctly answer that a dose was being delivered when the light (light emitting diode, LED) was continuously lit. The percentage of nurses answering this question correctly increased to 94% among nurses who provided care for more than 10 patients treated with IONSYS. Correct identification of the administered dose also improved with increasing experience with patients treated with IONSYS, from 69% among nurses who had treated 1 to 3 patients to 92% among nurses who had treated more than 10 patients.

On balance, the clinical data demonstrate that the learning curve among nurses who care for patients treated with IONSYS will require them to be closely supervised for the first 10 patients to become proficient with the system.

A deficiency is that a clear and practical mechanism to dispose of unused fentanyl contained in IONSYS has not been demostrated. This is an important omission because the novel formulation of fentanyl does not lend itself to routine disposal and the high residual quantity of fentanyl in used IONSYS units poses a significant risk for diversion.

The overall therapeutic benefit of IONSYS to post operative patients is superior to placebo ans similar to IV PCA despite quantitative differences in the dosing of rescue opioid in the early post-operative period. Therefore, while IONSYS may present operational advantages over IV PCA because of the product's simplicity, the benefit over IV PCA to an individual post-surgical hospitalized patient does not appear to be therapeutically significant.

On balance, IONSYS does offer a clinical benefit to post surgical patients provided that the supervision of nurses is adequate during their early experience with the product and that the method of disposal does not create a risk to the public health.

1.3.1 Brief Overview of Clinical Program

In this submission, the sponsor provided clinical safety data from two US studies (CAPSS-319 and CAPSS-320) and a single EU study (FEN-PPA-401) that in conjunction with the database from the original NDA are intended to support the safe use of IONSYS, previously referred to as the E-TRANS® (fentanyl HCl) system. (When tables included in this review were abstracted as pictures from the Sponsor's submissions, IONSYS is sometimes referred to as E-TRANS). These studies were conducted in postoperative adult patients following major orthopedic, abdominal or pelvic surgery. In these studies, both the patient instructions for the IONSYS system use and the pharmacist's instructions for product performance testing (i.e., to establish system functionality prior to dispensing) were evaluated. In addition, the evolution and testing of product information and performance testing materials for patients, nurses, and pharmacists are described to support the use of the IONSYS) system by the patient and health care provider.

1.3.2 Efficacy

Analysis of efficacy was performed in the previous review cycle and will not be duplicated here. In summary, IONSYS provided a statistically significant greater treatment effect when compared to placebo in the analyses of both the Evaluable and ITT populations. An exception occurred in Study 008, in the analysis of the ITT population. The cause for this finding was related to a high drop-out rate during the first three hours of study drug application. This high drop-out rate was attributed to inclusion of patients whose pain had not been adequately treated prior to system application. A post-hoc analysis performed by the Division as part of the previous review cycle excluded these patients and discovered a statistically significant treatment effect for the study drug.

Summary of Efficacy Findings from First Cycle NDA Submission September 23, 2003

	Dropouts due to lack of efficacy			Dropouts for any reason		
Study #	E-TRANS	Placebo	p-value	E-TRANS	placebo	p-value
C-95-016						
All-treated:	6/77 (8%)	9/25 (36%)	.0005	9/77 (12%)	12/25 (48%)	<.001
Evaluable:	6/77 (8%)	9/22 (41%)	.0001	9/77 (12%)	9/22 (41%)	.0017
C-2000-008						
All-treated:	48/154 (31%)	23/51 (45%)	.07	58/154 (38%)	29/51 (57%)	.0162
Evaluable	36/142 (25%)	19/47 (40%)	.0486	46/142 (32%)	25/47 (53%)	.0107
C-2001-011						
All-treated:	70/244 (29%)	144/240 (60%)	<.0001	90/244 (37%)	164/240 (68%)	<.0001
Evaluable:	64/235 (27%)	116/204 (57%)	<.0001	81/235 (35%)	128/204 (63%)	<.0001

Table was copied from page 7 of Team Leader Memo July 15, 2004 by Cecila Winchell, M.D..

The secondary outcome measures were also generally supportive of a finding of effective analgesia for IONSYS.

1.3.3 Safety

The overall safety database includes 1763 subjects exposed to IONSYS with a 40 mcg system.

The mean number of doses subjects who were treated with a 40 mcg IONSYS system in controlled trials and studies was 38, with a range of 0 to 208 doses. Two hundred and ninety-seven subjects were administered two or more systems and obtained up to 208 doses.

No subjects died during treatment with IONSYS. Five subjects died after completing or withdrawing from earlier studies and were evaluated in the previous review cycle. IONSYS did not appear to be a likely direct or indirect cause of the death of these patients. Among the patients participating in the new studies that included in the current submission (CAPSS 319, CAPSS 320, and FEN-PPA-401) there were 3 deaths in the IV PCA treatment arm, but no patients exposed to IONSYS died.

The rates of discontinuation due to adverse events were lower in the IONSYS 40 mcg treatment groups 35 (4.4%) in the original studies, 42 (4.3%) in the new studies (77/1763 [4.4%] overall) than in the IV PCA morphine treatment groups (86/1313 [6.5%]). Few patients also discontinued for adverse events in the placebo groups (7/316 [2.2%]).

Serious adverse events and common adverse events were those that would be expected in post-surgical patients and/or patients treated with opiates. No unusual events or events occurring at a higher rate than would be expected in the post-surgical setting were found, with the exception of application site reactions. These reactions were generally not severe and were reversible. Information regarding application site reactions should be provided to prescribers, especially in anticipation of the fact that patients may be treated consecutively with multiple systems, which could exacerbate these dermatologic effects.

1.3.4 Dosing Regimen and Administration

IONSYS provides a nominal 40 μg dose of fentanyl (base equivalent) per activation, which is delivered over a 10-minute period with a current of 170 μA. To initiate administration of a fentanyl dose, the patient must press the recessed button on the top of the system firmly twice within 3 seconds. An audio tone (beep) indicates the start of delivery of each dose, and a red light from a light-emitting diode (LED) remains on throughout the 10-minute dosing period.

A maximum of 6 x 40 mcg doses per hour can be administered by the IONSYS system. Each system operates for 24 hours, or until 80 doses have been administered, whichever occurs first. The system becomes inoperable after this period. The maximum amount of fentanyl that can be administered from a single system over 24 hours is 3.2 mg (80 individual 40 mcg doses). The system incorporates an automatic feature to terminate drug administration if error conditions are detected.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted for IONSYS.

Titration to Comfort
Listings from pre-enrollment medications indicate that the opioids used included fentanyl, morphine, hydromorphone, and sufentanil, (meperidine was allowed in limited doses for shivering only). In active-controlled studies (CAPSS-319, CAPSS-320, and FEN-PPA-401), a maximum opioid dose equivalent to IV morphine 40 mg was allowed to titrate to comfort (pain intensity ≤4/10) during the immediate postoperative period to exclude patients with very severe pain and/or high opioid requirements.

Supplemental Analgesic Medication

Supplemental IV opioids (rescue medication) were provided as needed during the first 3 hours of each IONSYS 40 mcg study. This time was limited to 3 hours to have a defined period when only IONSYS fentanyl was used for analgesia (3-24 or 72 hours). In all controlled studies, 444/1763 (25.2%) patients in the IONSYS group and 212/1313 (16.1%) in the IV PCA morphine group received rescue medication.

- In the IONSYS 40 mcg group, 328 patients received supplemental fentanyl (mean total of 96.5 mcg), and 125 patients received supplemental morphine (mean amount 6.6 mg) during the first three hours after treatment initiation.
- In the IV PCA morphine group, 7 patients received supplemental fentanyl (mean amount of 75.0 mcg) and 207 patients received supplemental morphine (mean amount of 6.6 mg).

The difference in supplementary rescue opioid between treatment arms is small and not relevant from a clinical perspective. It is notable that, unlike IV PCA, IONSYS does not enable patient care providers to administer rescue analgesic doses from the device itself.

1.3.6 Special Populations

Elderly
A total of 499 patients ≥65 years of age used IONSYS in a controlled study. Of these 499 patients, 174 were ≥75 years old (75-90 years old). The majority of the elderly patients who used IONSYS 40 µg were female (56.9%); most were Caucasian (91.2%) and entered following orthopedic bone (61.7%) or lower abdominal surgery (29.1%). A higher proportion of elderly patients (29.2% [79/271]) had severe systemic co-morbidities (ASA III) compared with all patients in controlled studies (12.5%). Demographics for patients in the IV PCA morphine and placebo groups were generally similar. Demographics for the 569 elderly patients (including 183 who were ≥75 years) who used IONSYS 40 µg in all clinical studies were similar to those of the elderly patients in the controlled studies.

Pediatric Patients
Pediatric safety data were obtained in

In the original NDA, ALZA Corporation requested a deferral of the pediatric rule [21 CFR 314.55 (b)] for IONYS use in pediatric patients ≥6 years old. ALZA also requested a waiver of the pediatric rule for IONSYS use in pediatric patients <6 years old, as discussed at the pre-NDA meeting of 18 January 2001.

Reviewer's comment: The use of patient controlled analgesia has been reported in pediatric patients as young as 6 years of age (http://www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/Nov2000.pdf, accessed 5/16/06).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

IONSYS (previously referred to as E-TRANS® fentanyl) is a noninvasive, self-contained, preprogrammed, patient-controlled analgesia (PCA) system that is applied to the upper arm or chest (Figure 2.1-1). Using iontophoresis (ie, the introduction of ions of a medicant into tissues by means of an electric current), IONSYS delivers drug transdermally for management of acute pain in adults requiring opioid analgesia. ALZA Corporation developed IONSYS as a needle-free alternative to current modes of patient controlled analgesia (PCA) for acute pain.

Figure 2.1-1 Depiction of IONSYS

From Sponsor's Figure A, NDA Summary page 10.

IONSYS delivers a nominal 40 mcg on-demand dose of fentanyl when the patient firmly presses the system's on-demand dosing button 2 times within 3 seconds. Each dose is delivered over 10 minutes, with a maximum of 6 doses/hour. During dose delivery, the system will not respond to additional dosing requests (ie, lockout). IONSYS has visible and/or audible indicators that signal the beginning and end of dose delivery, the approximate number of doses delivered, and operational problems. The system remains functional for 24 hours or until 80 doses are delivered (whichever comes first). It then becomes inoperable and does not respond to additional dose requests; it is to be discarded in accordance with appropriate institutional policies for Schedule II substances.

2.2 Currently Available Treatment for Indications

Short-term, acute postoperative pain in hospitalized adult surgical patients requiring opioids is currently managed with patient controlled analgesia (PCA) administered intravenously (IV).

2.3 Availability of Proposed Active Ingredient in the United States

Fentanyl is currently available in the USA as an injectable solution, as a transdermal patch, and as an oral lozenge.

2.4 Important Issues with Pharmacologically Related Products

As a synthetic phenylpiperidine opioid agonist, fentanyl may be expected to cause the following systemic effects: analgesia, respiratory depression, emetic effects with or without accompanying nausea, antitussive effects, decreased peristalsis and transient hyperglycemia. Opioids have

distinct effects on the central nervous system and may cause miosis, increased parasympathetic activity and/or sedation. The common side effects of fentanyl include nausea, vomiting, constipation, somnolence, and diaphoresis. The most serious risk is respiratory depression.

Drug-drug interactions have been identified with inhibitors of cytochrome P450 and/or isoenzyme 3A4.

2.5 Presubmission Regulatory Activity

- January 27, 1993 The IND for Fentanyl Electrotransport System was filed.

- April 1996 A closed meeting of the ALSDAC was held to discuss the development plan for ETRANS as well as proprietary information on the mechanics of the device, including the electrophysiological tests done to provide consistent drug delivery. The information provided was deemed adequate.

- February 18, 1999 An End of Phase 2 meeting was held.

The following agreements were made:

- Two AWC studies were needed to provide basis for the claim of pain control in the acute postoperative setting
- A controlled pediatric efficacy trial was not required but the pediatric trials should define the appropriate starting dose and a titration scheme, should evaluate the PK in this population, and should include a good cross-section of ages within the stated range of 6-17 years.
- Population PK data would be obtained from one US study involving approximately 300 patients.
- The overall safety database of 2000 patients , including 120 pediatric patients and 75-95 patients over 65 years, appeared acceptable.

- April 28, 1999 An advice meeting was conducted to clarify CMC issues for E-TRANS fentanyl.

  The Division clarified the following points from the February 1999 meeting:

- The indication for this product sought is "

- The intent of the blood sampling in the US studies was for documentation of fentanyl delivery and not for population PK analysis.

- January 18, 2001 A pre-NDA meeting was held with ALZA.

The following comments were made:

- Data on the safety of maximal exposure to the 40 mcg dose should be provided. Clinical Review Section
- The Division had "no concerns related to the waiver request for children under 6 years."
- ALZA was told that the following device related issues had to be addressed at the time of NDA submission:
- Demonstration that the device remains reliable throughout its shelf life e.g. shuts off properly after administration of a single dose, after administering 6 doses in an hour and after administration of 80 doses
- Demonstration of a 0% failure rate for the critical performance parameters of the device, e.g. delivery of the correct amount of fentanyl
-
-
- A risk management plan was to be submitted, including special instructions for the physician, patient, advertising and promotion.

- February 6 2001

  The Division sent an advice letter stating that [redacted] was not considered safe. '[redacted]. You may wish to consider continuing with the development of the 40 mcg [redacted] restricted to the hospital setting where the opioid naïve post-operative patient can be adequately monitored."

- May 12, 2001

  ALZA submitted a response to the minutes from the January 18 2001 meeting. The following changes were requested and clarifications were made:

- Device label and device manuals were not to be provided since E-TRANS was determined to be a drug product.
- The Division was told that a pharmacokinetic study would be planned to determine the result of patients receiving the maximal amount of doses (n=80) in the minimum amount of time (13.33 hours).
-

- June 6 2001

  A Type A meeting was held with ALZA.

  - The division indicated that the major obstacles to ALZA's current development plan for E-TRANS were 1) and 2) need for safety data on the higher and maximum number of 40 mcg dose activations.
  - ALZA indicated that in PCA systems safety is the sum of the safety of the delivery system, the drug delivered and the patient experience of pain...ALZA's current safety database indicates that the number of subjects using more than 70 activations represent only 5% of the total population investigated. ALZA proposed studying the safety of using the higher and maximum number of activations as a post-marketing commitment.
  - ALZA indicated that their intention is to launch the 40 mcg dose in a medically supervised setting. The Division indicated that this setting would help to provide adequate safety monitoring and the review of the application would determine the adequacy of the safety of the product using the higher or maximum number of doses.
  - A risk management program was to be implemented at the time of the NDA approval. It should include

- An NDA application was submitted September 23, 2004

  The Division's Approvable letter issued for NDA 21-338 on July 23, 2004 noted two clinical requirements that needed to be fulfilled before the product could be approved.

  - The first requirement is:

a. Clinical data supporting the safe use of the Patient and Health-Care Provider product instructions for use and the instructions for product performance testing

In a September 10, 2004 meeting to discuss the requirements of the approvable letter, the Division suggested that an 'actual-use" study was appropriate to assess the safe use of the intended labeling for patients, health care providers and pharmacists. In the subsequent November 23, 2004 letter, the Division clarified that a complete study report containing data from the ongoing CAPSS 319 and CAPSS 320 studies with focused and in-depth discussion of the in-use database would be might be sufficient in lieu of the "actual-use" study suggested at the September 10, 2004 meeting.

Instruments presented in the current submission to evaluate product instructional materials included:

(1) patient and nurse ease-of-care questionnaires, included in the phase 3b study protocols;

(2) patient, nurse, and pharmacist surveys, conducted in conjunction with the 2 US-based phase 3b studies but not part of the study protocols; and

(3) qualitative and quantitative research on patient and healthcare professional instructional and educational materials for the IONSYS) system that directed changes resulting in improvements to the materials used in the phase 3b program and to the final patient, nurse, and pharmacist guides for use of the IONSYS) system.

- The second clinical requirement stated in the Division's Approvable letter issued for NDA 21-338 on July 23, 2004 is:

b. Clinical data evaluating conversion from and adjunctive therapy with other opioid analgesics during the early treatment phase with Ionsys system.

The Division clarified in the September 10, 2004 meeting that the detailed information regarding proper patient selection for use of the IONSYS) system as well as instructions for providing access to supplemental injectable analgesia during the use of the IONSYS) system was needed in the product labeling.

2.6 Other Relevant Background Information

Patient Selection
The types of surgeries included in the new studies are representative of a general surgical patient population, predominantly orthopedic, pelvic, and abdominal surgeries. Studies also included thoracic surgeries but are a small proportion of the study population because these procedures are less common in practice. Analysis by type of surgery indicates that the use of the IONSYS) system in the general surgical population does not present a particular risk in the subgroups. Other patient characteristics such as age <65 years or 65+ years and gender did not present different safety signals compared to overall study population when using the IONSYS) system. Certain categories of patients were not included in the studies: ASA IV patients, non-

adult patients, and opioid tolerant patients. Patients who were opioid tolerant or required significant opioids during titration to comfort (i.e., >40 mg morphine equivalent) prior to enrollment were not included in the study because supplemental opioids were not allowed after Hour 3 in the research protocol and the small doses of fentanyl provided by the IONSYS) system may not meet the analgesic requirements of opioid tolerant patients.

Titration to Comfort

IONSYS is a patient controlled analgesia system using fentanyl in repeated, small doses intended to maintain analgesia after patients have achieved an acceptable level of comfort with titrated IV opioids. Listings from pre-enrollment medications indicate that the opioids used included fentanyl, morphine, hydromorphone, and sufentanil, (meperidine was allowed in limited doses for shivering only). In active-controlled studies (CAPSS-319, CAPSS-320, and FEN-PPA-401), a maximum opioid dose equivalent to IV morphine 40 mg was allowed to titrate to comfort (pain intensity ≤4/10) during the immediate postoperative period to exclude patients with very severe pain and/or high opioid requirements.

Supplemental Analgesic Medication

Supplemental IV opioids (rescue medication) were provided as needed during the first 3 hours of each IONSYS study. This time was limited to 3 hours to have a defined period when only IONSYS was used for analgesia (3-24 or 72 hours) although usual and customary patient controlled analgesia practice outside of clinical studies usually allows the use the supplement IV opioid. In most of the controlled studies, IV fentanyl was used for patients receiving IONSYS or placebo systems (or IV morphine during a national shortage of IV fentanyl) and IV morphine was used for patients receiving IV PCA morphine. In Study FEN-PPA-401, IV morphine was used for both treatment groups. In all controlled studies, 444/1763 (25.2%) patients in the IONSYS group and 212/1313 (16.1%) in the IV PCA morphine group received rescue medication. In the IONSYS group, 328 patients received supplemental fentanyl (mean total of 96.5 µg), and 125 patients received supplemental morphine (mean amount 6.6 mg) during the first three hours after treatment initiation. In the IV PCA morphine group, 7 patients received supplemental fentanyl (mean amount of 75.0 µg) and 207 patients received supplemental morphine (mean amount of 6.6 mg). In the active controlled studies (CAPSS-319, CAPSS-320, FEN-PPA-401, and **C-2000-007**), the proportion of combined patients requiring supplemental opioid medication was similar between IONSYS (228/1288 patients; 17.7%) versus IV PCA morphine (212/1313 patients; 16.1%). The supplemental opioid dosing used in Hours 0-3 for IONSYS was compared to IV PCA morphine in these active controlled studies. In CAPSS-319, CAPSS-320 and **C-2000-007**, patients received either supplemental fentanyl or morphine. The mean amount of fentanyl and morphine supplementation for IONSYS and IV PCA morphine were similar within each of the individual studies. In study FEN-PPA-401, morphine was the only allowed opioid for supplementation and the mean amount of morphine was similar between the IONSYS and IV PCA morphine (7.5 mg vs. 6.5 mg, respectively).

The risks associated with the clinical use of IV PCA have been reviewed by the Department of Veterans Affairs (VA) National Center for Patient Safety using Hazard Analysis and Critical Control Point (HACCP) methodology originally developed by FDA (http://www.patientsafety.gov/SafetyTopics/HFMEA/HFMEA_JQI.pdf. and http://www.hospitalconnect.com/medpathways/tools/content/2_A.pdf).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and CDRH

CMC
In the previous review cycle the primary stability batches (registration lots) had a particularly high rate of out-of-box failures (— which was also attributed to —— ' — Therefore, corrective action lots were manufactured —— — but systems failed to deliver the required dose, or skipped doses. A total of — systems failed to pass electronic function test (Push button test). Review of the provided data could only justify a — expiration date from the date of manufacture. The design of the product ——

Other product quality issues in the development program for IONSYS included:

After the analysis of non-initiating systems in the current submission, the applicant made *Proof of Concept (POC)* batches ——

. Based on the analysis of the provided data, 6 month expiration date is justified for POC batches.

The proposed product label ——

CDRH

A review of the current submission was completed on April 24, 2006. The device-related deficiencies that were previously identified were generally resolved. Remaining issues were felt to be minor and able to be addressed during a post-market inspection.

3.2 Animal Pharmacology/Toxicology

No indications for fentanyl metabolizing activity in the skin were present, suggesting that fentanyl was absorbed through the skin unchanged. In recent studies non-ionized fentanyl showed a relatively high penetration through the lipid-rich stratum corneum, but the viable skin appeared to be a stronger barrier to absorption. With iontophoresis or electroporation (of an ionized fentanyl solution), penetration of the hydrophilic viable skin was increased compared to passive diffusion of non-ionized fentanyl. By changing the delivery mode of the current (e.g., voltage, duration and number of pulses), control of the quantity of fentanyl transported through the skin can be obtained.

The main toxicological finding, other than expected opioid effects, include mild to moderate skin irritation with a study of experimental sensitization in the hairless guinea pig (TR-92-1561-022). The results of this study in hairless guinea pigs indicate that electrically-assisted delivery of fentanyl (anode) at a maximum dose of 1.1 mg/kg/8 h and the maximum current density of 0.1 mA/cm^2 be placed in the mild to moderate sensitizer category. These exposures are in excess of what would be obtained from proper clinical use of IONSYS.

Dr De of the pharmacology/toxicology review team indicated that qualification of impurities, however, will be required prior to approval. This may be accomplished by either a reduction in the specifications for the following impurities in the drug substance or adequate qualification for safety of the compounds:

Dr. De of the pharmacology/toxicology team advises imposing a limit of NMT — , each for these impurities in the drug substance. Alternatively safety of the proposed levels may be demonstrated if these — are human metabolites, or by two genotoxicology studies; one in vitro mutation assay such as Ames bacterial mutagenicity assay and the other an

in vitrocytogenetic assay. Studies should achieve the limit doses for these assays with the isolated impurities. If the impurities are mutagenic, provide the impurities should be limited to < — or an assessment of carcinogenic potential in a standard 2-year model or an appropriate alternative model should be provided.

In summary, adequate qualification of several impurities via 14-day repeat dose toxicology studies and a minimal genetic toxicology screen are needed, as described in ICHQ3A and ICHQ3BR. Alternately, the stability specifications should be reduced.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor submitted three new clinical studies. These studies were randomized, but not blinded and do not provide new efficacy information to support of the previous submission. The studies do report new clinical data intended to support safety of the product and purport to evaluate the Patient and Health–Care Provider product instructions for use.

The new open-label clinical studies also describe use of the product with other pain medications including opioids commonly used in the early post-operative to supplement analgesia in patients who are inadequately treated by PCA.

4.2 Tables of Clinical Studies

Table 4.2-1: New Studies Included With Current Submission

Study Name	Number of patients randomized	Study duration	Data[a]
CAPSS319	799 patients, 395 active, 404 IV morphine PCA	≥ 24 hours and < 72 hours	S
CAPSS320	506 patients, 252 active, 254 IV morphine PCA	≥ 24 hours and < 72 hours	S
FENPPA401	660 patients, 325 active, 335 IV morphine PCA	≥ 24 hours and < 72 hours	S

[a]Code: S-safety, E-efficacy, P-pharmacokinetics, W-wear

The duration of these studies was to be at least 24 hours or a maximum of
The Patient Ease-of-Care Questionnaire. Pain Management Goal, Nurse Ease-of-Care Questionnaire, Physical Therapist Ease-of-Care Questionnaire, Assessment of the Adherence of the IONSYS, Non-Routine Events Checklist, Post-Study Analgesics.

Listing of clinical trials from NDA Submission of June 17, 2004. The pivotal trials are in **bold** font. The trials that were stopped prematurely are in *italic* font.

Table 4.2-2: Trials included with Submission of June 17, 2004.

Trial name	Number of patients randomized	Study duration	Data[a]
C-95-016	102 patients: 77 active, 25 placebo	24 hours	S,E
C-2000-008	205 patients:154 active, 51 placebo	24 hours	S,E
C-2001-011	484 patients: 244 active, 240 placebo	24 hours	S,E
C-2000-007	636 patients: 316 active, 320 morphine PCA	24 hours	S,E
C-2000-005	121 patients: all active	72 hours	S
C-2000-006	95 patients: all active	72 hours	S
C-2000-009	358 patients: all active	48 hours	S
C-93-023	253 patients: all active	48 hours	S
C-94-043	115 patients: all active	48 hours	S
C-95-019	78 patients: all active	48 hours	S
C-96-020	102 patients: all active	48 hours	S
FEN-INT-006	150 patients: all active	24 hours	S,P
C-92-038	14 patients: all active	24 hours	S,P
C-93-019	34 patients: all active	24 hours	S,P
C-94-060	70 patients: all active	24 hours	S,P
C-94-067	35 patients: all active	24 hours	S,P
C-94-068	28 patients: all active	72 hours	S,P
C-96-009	36 patients: all active	24 hours	S,P
C-97-001	40 patients: all active	24 hours	S,P
C-98-013	30 patients: all active	24 hours	S,P
C-2001-009	31 patients: all active	24 hours	S,P
C-2002-027	28 patients: all active	24 hours	S,P
C-2001-006	25 patients: all active	24 hours	P
C-95-034	24 patients	24 hours	S,W
C-95-050	24 patients	24 hours	S,W
C-95-051	24 patients	72 hours	S,W
C-95-053	24 patients	24 hours	S,W
C-96-003	111 patients	24 hours	S,W
C-94-057	83 patients	72 hours	S
C-94-058	85 patients	72 hours	S
C-94-059	21 patients	24 hours	S
C-96-055	27 patients	50 hours	S
C-96-056	8 patients	72 hours	S
C-96-057	3 patients	72 hours	S

[a]Code: S-safety, E-efficacy, P-pharmacokinetics, W-wear

4.3 Review Strategy

Electronic files along with case report tables (CRTs) and case report forms (CRFs) were reviewed in whole or in part. The study protocols, study reports and study results were reviewed for all supporting studies. The ISS was reviewed in depth. The data in the tables was compared with the data in the appendices. Each death was tracked backwards from the ISS through the appendices, narratives, CRTs and CRFs. Data points from a random sample of adverse events were followed through the appendices, CRTs and CRFs. ALZA's information on financial disclosure was reviewed.

The division files for IND 41,574 were reviewed. The electronic New Drug Application (eNDA) submissions dated September 23 2003, November 14 2003, March 25 2004, and April 2 2004, April 16 2004, April 30 2004, May 13 2004, June 4 2004, June 11 2004, and July 1, 2004 were also reviewed.

4.4 Data Quality and Integrity

No DSI audit was done as part of the clinical review. The data from most of the key tables in the study reports were cross-referenced with the study report listings and data from patient case report forms.

4.5 Compliance with Good Clinical Practices

The trials were conducted in accordance with accepted ethical standards.

4.6 Financial Disclosures

Study

Financial disclosure information was not obtained for 15 of the investigators and subinvestigators who conducted this study. The sponsor has submitted form 3455 for subinvestigator indicating his equity interest exceeding $50,000 of Johnson and Johnson stock in retirement plans and mutual funds. His site enrolled 3 of the patients in this study. was also reported by the sponsor to have an equity interest exceeding $50,000 of Johnson and Johnson stock in retirement plans and mutual funds. The site where Dr. conducted enrolled one patient.

Study

Financial disclosure information was not obtained for 18 of the investigators and subinvestigators who conducted this study. was reported by the sponsor to have an equity interest exceeding $50,000 of Johnson and Johnson stock in retirement plans and mutual funds. The site where Dr. conducte enrolled 20 patients. reported that a subsidiary of Johnson and Johnson provided a grant in support of the a site which recruited 22 patients. Dr

disclosed that he received over $25, 000 in honoraria for journal editing and reviews. His study site enrolled 4 patients.

Study FEN-PPA-401

Financial disclosure information was not obtained for 19 of the 193 investigators and subinvestigators who conducted this study.

Reviewer's comment: Investigators and subinvestigators who did not submit financial disclosure information or reported financial interests in Johnson and Johnson were each associated with a small number of patients so that it is unlikely that that the reported findings could have been biased by their participation.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new pharmacokinetic studies were presented with this submission. In the previous cycle, reports from clinical pharmacokinetic studies were evaluated to compare absolute bioavailability of fentanyl following application of different IONSYS systems capable of delivering 100– 230 µA of direct current (Studies C-96-009, C-97-001, C-94-068, C-2001-009, C-2002-027). Upon comparison with the pharmacokinetics of fentanyl following intravenous bolus administration, the sponsor determined that IONSYS systems employing 100, 140, 170, 200 and 230 µA deliver a transdermal fentanyl dose of 24.8, 35.1, 39.5, 49.5 and 53.9 mcg, respectively. The dose of fentanyl delivered *in vivo* was found to correlate with the amount of direct current employed by the IONSYS system. IONSYS with a170 µA fentanyl HCl system, capable of delivering 40 mcg of fentanyl was developed as the commercial formulation.

Pharmacokinetics of fentanyl following different sequences of on-demand dosing with IONSYS was studied. In comparison with IV bolus administration, fluctuations of fentanyl concentrations are small and therapeutic concentrations are achieved slowly. Passive absorption of fentanyl, equivalent to 16 to 192 mcg (over 24 hours), was observed following a 24 hour application (mean 2.3 mcg/hr) of the commercial formulation of IONSYS 40 mcg system without activation (C-2002-027). Fentanyl pharmacokinetics is dose-dependent in that increase in elimination half-life of fentanyl was observed between one-day and three-day on-demand dosing regimen. The AUC of fentanyl increases with the more frequent administration and steady state levels are achieved at approximately 60 hours following two on-demand doses every 4 hours.

Fentanyl AUC following a single 24-hour application and on Day 3 following three consecutive 24-hour applications (each applied to a new skin site) of the system were similar, suggesting no change in fentanyl kinetics with repeated 24-hour applications, with each application made to a new skin site.

The delivery of fentanyl from IONSY is similar whether applied on the upper outer arm or the chest. When the system is placed on the lower inner arm, the delivery of fentanyl is approximately 20% lower.

5.2 Pharmacodynamics

Study FEN-INT-006 evaluated the safety and efficacy of IV infusion (over 10 minutes) of fentanyl 20, 40 and 60 µg delivered by Patient Controlled Analgesia (PCA) to 150 patients with moderate to severe pain after major abdominal surgery. It was observed that patients receiving 40 mcg of fentanyl IV infusion of 10 minutes had satisfactory analgesia in comparison with the subjects receiving lower dose of 20 mcg. In addition, the number of adverse events was lower in this treatment group in comparison with the subjects receiving

fentanyl 60 mcg/dose. Hence, this study served as a proof of concept for developing the IONSYS 40 mcg/dose system. Observations from this study with regard to exposure-response of fentanyl indicated strong evidence of a dose-effect relationship based on both the patient global response and the visual analog scale. However, no correlation wasobserved between measures of pain relief or respiratory depression, and fentanyl concentration.

5.3 Exposure-Response Relationships

IONSYS was studied in a pilot multicenter, open-label study (C-93-023) to compare safety and efficacy of PCA fentanyl doses of 25 mcg and 40 mcg in patients expected to have moderate to severe pain after surgery performed under general or regional anesthesia. The results demonstrated that the 40 mcg dosing regimen provided better efficacy than the 25 mcg dosing regimen because 40 mcg dosing was associated with fewer on-demand doses and IV supplements as compared to the 25 mcg dosing regimen. In addition, VAS scores for pain intensity were lower during the first 6 hours and mean fentanyl concentrations were higher with the 40 mcg dosing regimen as compared to 25 mcg.

The postoperative analgesic effects of 3 demand dose sizes of fentanyl administered by IV PCA (20, 40, and 60 mcg) were investigated in a multicenter,double-blind, randomized, parallel-group trial (Study FEN-INT-006) in patients with moderate to severe pain after major abdominal surgery performed under general anesthesia. Results from Study FEN-INT-006 were consistent with those of Study C-93-023. Study FEN-INT-006 also provided evidence of a dose-effect relationship based on both the patient global response and the visual analog scale. The number of fentanyl demands made during the study was significantly lower with both 40 μg and 60 mcg dose levels as compared to the 20 mcg dose level. There was no significant difference in the number of fentanyl demands between the 40 mcg and 60 mcg dose levels.

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6 INTEGRATED REVIEW OF EFFICACY

In the review of the previous submission, the Division determined that efficacy had been established for the proposed indication. The current submission contains only open label studies comparing IONSYS to IV morphine PCA. They were not reviewed to further establish efficacy of the proposed product.

The Division Director's Memo of July 23, 2004 by Bob Rappaport, M.D. included the following synopsis with references to the reviews by Elizabeth McNeil M.D., (medical officer) and Celia Winchell, M.D. (Team Leader):

"**Studies C-95-016 (016), C-2000-008 (008) and C-2001-011 (011):** These three studies were single-application, randomized, placebo-controlled, double-blind, parallel-group trials comparing E-TRANS to placebo, performed in patients with post-operative pain. Subjects were adults requiring at least 24 hours of opioid treatment post-operatively, who were to have been titrated to a comfortable level of pain control with IV opioids in the PACU. Subjects were then randomized to receive a single application of E-TRANS or matching placebo for use during the first 24 hours post-operatively. IV fentanyl administration was permitted during the first three hours after study drug application. Subjects were considered to have completed the study after 24 hours from study drug application or after 80 doses had been delivered, whichever came first.

The primary efficacy outcome was defined as the number of patients in each treatment group who dropped out of the study more than three hours after initiation of therapy due to inadequate pain control. The secondary outcome measures included: pain intensity, patient global assessment, investigator global assessment, number of on-demand doses delivered, number of patients requiring re-titration to comfort, and assessment of the adherence of the E-TRANS system

The clinical reviews include thorough presentation and discussion of subject disposition. No significant concerns were identified. However, the protocol-defined analyses called for using an Evaluable population of subjects who discontinued only for lack of efficacy. Drs. McNeil and Winchell have also considered an ITT population in their analyses. This population consists of subjects who dropped out for any cause. I concur that this type of analysis is essential, as subjects who dropped out due to drug-related adverse events in particular should be considered treatment failures for a drug designed to treat a subjective symptom such as pain.

The table below, copied from page 7 of Dr. Winchell's review, summarizes the results of the primary efficacy analyses for the three trials.

	Dropouts due to lack of efficacy			Dropouts for any reason		
Study #	E-TRANS	Placebo	p-value	E-TRANS	placebo	p-value
C-95-016						
All-treated:	6/77 (8%)	9/25 (36%)	.0005	9/77 (12%)	12/25 (48%)	<.001
Evaluable:	6/77 (8%)	9/22 (41%)	.0001	9/77 (12%)	9/22 (41%)	.0017
C-2000-008						
All-treated:	48/154 (31%)	23/51 (45%)	.07	58/154 (38%)	29/51 (57%)	.0162
Evaluable	36/142 (25%)	19/47 (40%)	.0486	46/142 (32%)	25/47 (53%)	.0107
C-2001-011						
All-treated:	70/244 (29%)	144/240 (60%)	<.0001	90/244 (37%)	164/240 (68%)	<.0001
Evaluable:	64/235 (27%)	116/204 (57%)	<.0001	81/235 (35%)	128/204 (63%)	<.0001

These results demonstrate that E-TRANS provided a statistically significant greater treatment effect when compared to placebo in the analyses of both the Evaluable and ITT populations. The only exception occurred in Study 008, in the analysis of the ITT population. Dr. Winchell clearly explicates the only plausible cause for this finding in her review. A high drop-out rate during the first three hours of wear appeared to account for the failure of the study drug to separate from placebo. This finding seems to be at least partially explained by the inclusion of patients whose pain had not been adequately treated prior to system application. A post-hoc analysis performed by the review team that excludes these patients did find a statistically significant treatment effect for the study drug. On page 16 of her review, Dr. Winchell concludes that:

> ...the results of this study further highlight the need to emphasize that ETRANS has been shown effective only in patients titrated to comfort prior to system application, and that a period of three hours of access to rescue medication is needed prior to reliance on the effectiveness of the transdermal system.

The secondary outcome measures were generally supportive of a finding of effective analgesia for E-TRANS.

Study C-2000-007 (007) was an open-label, active-control study comparing E-TRANS to IV PCA morphine in the post-operative setting. E-TRANS did not show a statistically significant advantage over IV PCA morphine in the primary outcome measure, Patient Global Assessment at 24 hours. This open-label, active-control study did not provide adequate control for the introduction of bias. Nor did it provide assay sensitivity to allow for an adequate assessment of efficacy in the absence of a finding of superiority of the study drug. Therefore, it is, by design, inadequate to support a finding of efficacy."

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Sponsor's electronic Integrated Summary of Safety Table was the primary source for this reviewer's analysis of adverse events. Adverse events data originating from the newly submitted Studies 319, 320 and 410 were abstracted from the ISS and pooled for this review. These data from 972 patients exposed to the sponsor's product were usually considered separately from the entire ISS database because the instructions for use of the product have changed since the original submission and the primary interests are to determine whether the instructional material enables safe use of IONSYS and whether other opioid analgesics can be used safely during the early treatment phase with the IONSYS system. Some of the summary tables of adverse events and drop-outs in this review also contain data from the entire ISS for comparison to the findings from the new studies.

7.1.1 Deaths

No deaths occurred in any of the 972 patients receiving IONSYS treatment in Studies CAPSS-319, CAPSS-320 or FEN-PPA-401. Three patients in the treatment group with IV PCA morphine, but their deaths did not appear to be a result of IV PCA.

In all clinical studies, none of the adult patients who received the IONSYS system died during a study. Three deaths (previously reviewed by Dr. Elizabeth McNeil) occurred after study termination, but were unrelated to study medication. One of these deaths occurred in a controlled study (respiratory failure secondary to a suspected pulmonary embolus in a 79-year-old male following ventral hernia repair) and 2 occurred in a stopped study (esophageal/diaphragmatic rupture and septic shock in a 64-year-old male following bowel resection surgery, and sepsis and pneumonia in a 66-year-old male following arthroplasty).

7.1.2 Other Serious Adverse Events

Serious adverse events were reported in 83 patients participating in CAPSS-319, CAPSS-320 and FEN-PPA-401. 40 (4%) patients were treated with IONSYS and 43 (6%) patients treated with IV PCA. The adverse events reported are typical of adverse events associated with opioids. The following table summarizes serious adverse events by body system. Serious adverse of the nervous system were predominantly undesirable changes in consciousness related to sedation. The total number of serious adverse events exceeds the sum of the serious adverse events listed by body system in the table below because only body systems most likely to be affected by the study product are included.

Table 7.1.2-1 Serious Adverse Events

Body System	Clinical Study	Summary

	CAPSS-319 N=799		CAPSS-320 N=506		FEN-PPA-410 N=660		Totals N=1965	
	IONSYS N=395	IVPCA N=404	IONSYS N=252	IVPCA N=254	IONSYS N=325	IVPCA N=335	IONSYS N=972	IVPCA N=993
Respiratory	3(1%)	3(1%)	1(<1%)	5(2%)	1(<1%)	4(1%)	5(1%)	12(2%)
Cardiovascular	6(2%)	2(1%)	3(1%)	4(2%)	0(0%)	4(1%)	9(2%)	10(1%)
Digestive	2(1%)	2(1%)	4(2%)	3(1%)	3(1%)	2(1%)	9(2%)	7(1%)
Skin	2(1%)	0(0%)	0(0%)	0(0%)	3(1%)	0(0%)	5(1%)	0(0%)
Nervous	2(<1%)	3(<1%)	1(<1%)	5(2%)	1(<1%)	4 (1%)	4 (<1%)	12(2%)
Total	18(5%)	18(5%)	12(5%)	16(6%)	10(3%)	10(3%)	40(4%)	44(6%)

Data were abstracted from Sponsor's electronic Adverse Event Table in the electronic Integrated Summary of Safety.

Among all controlled clinical and studies there were 74 (4.2%) serious adverse events reported for the 1763 patient exposed to IONSYS. The distribution of serious adverse event by body system is similar among all controlled clinical trials and studies to the distribution for studies CAPSS-319, CAPSS-320 and FEN-PPA-401 listed in Table 7.1.2-1 above.

The narratives of serious respiratory events associated with IONSYS were examined by this reviewer for possible causality. Respiratory adverse event were specifically reviewed because of the known relationship of opioids, including fentanyl, to depression of respiratory drive. Of the 5 patients in the new studies who experienced a respiratory SAE, 3 patients, all in Study CAPSS-319, experienced the SAE while using IONSYS.

1) Patient No. 55004 experienced hypoventilation 0.5 hours after enrollment that lasted for 4.6 hours and was treated with naloxone. At the time of the event the patient had not yet initiated a dose.

Reviewer's comment: This SAE is unlikely to have been related to treatment.

2) Patient No. 42027 experienced hypoxia 6.8 hours after enrollment that lasted for approximately 19 hours. At the same time, the patient was experiencing atrial fibrillation with a rapid ventricular response.

Reviewer's comment: This event was likely related to the cardiac dysrhythmia rather than central depression of ventilation by fentanyl.

3) Patient No. 22017, a 65 year old woman with a history of exertional dyspena and myocardial infarction experienced dyspnea 3.1 hours after enrollment that lasted for over an hour and was treated with naloxone and nitroglycerine. The patient had been recently emerged from general anesthesia about 5 hours earlier and been recently been treated with Phenergan 25 mg for nausea. She was given 12.5 mg of meperidine and 36 mg of morphine in the post-operative period. It appears that IONSYS had been placed prior to the episode of respiratory distress, and displayed a single flash to indicate the number of doses administered. The Sponsor's narrative summary indicates that IONSYS had not been activated.

Reviewer's comment: The episode of respiratory distress may have been related to concomitant medication including Phenergan and opioids. The patient's surgeon attributed the episode to Phenergan. Meperidine was likely administered for shivering in the immediate post-operative period and IV morphine to control pain. While the etiology of this episode cannot be determined with certainty, IONSYS appears to have had a minor role at most.

The remaining 2 patients using IONSYS who experienced a respiratory SAE, experienced the SAE after removal of the IONSY system.

4) Patient No. 10784 (Study FEN-PPA-401) experienced hypoxia approximately 5 hours after removal of IONSYS system.

Reviewer's comment: This event is unlikely to have been related to treatment because of the long latency after the last treatment with IONSYS and may have been related to a concurrent second event of intestinal hemorrhage. Both events resolved 30 days later.

5) Patient No. 39008 (Study CAPSS-320) experienced pneumonia occurring 13 days after enrollment. The event resolved approximately 35 days later.

Reviewer's comment: It is unlikely to have been related to IONSYS.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Among the 972 patients treated with IONSYS in Studies CAPSS-319, CAPSS-320 and FEN-PPA-401, 141 (15%) did not complete the study as compared to 993 patients treated with IV PCA with 124 (12%) patient discontinuing the study before completion. Of the 141 patients treated with IONSYS who discontinued, 42 patients (4%) experienced an adverse event compared with 68 (7%) patients having an adverse event in the IV PCA group. Among all patients treated with IONSYS in the ISS (N=1793), there were 380 (22%) patients who discontinued early with 77 (4%) of these patients discontinuing because of an adverse event. Of the 1313 patients treated with IV PCA in the ISS, 204 (16%) patients discontinued early, with 87 (7%) leaving because of an adverse event.

In the new studies and in the entire ISS most patients who were treated with IONSYS and withdrew from their study early did so because of inadequate analgesia. Among all studies, the frequency of dropouts because of inadequate analgesia was nearly three times higher among the IONSYS treated patients (n=249, 14%) relative to the patient in the combined comparator arms (n= 68, 5%). The frequency of dropouts because of inadequate analgesia was about twice as high in the IONSYS treatment group (n=77, 8%) compared to the IV PCA treatment group

(n=68, 4%) in the new studies presented in this submission. The following table summarizes these findings.

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			
	Original (n=791)	New (n=972)	Combined (n=1763)	Original (n=320)	New (n=993)	Combined (n=1313)	Placebo (n=316)
Completed study	552 (69.8%)	831 (85.5%)	1383 (78.4%)	240 (75.0%)	869 (87.5%)	1109 (84.5%)	111 (35.1%)
Completed allowable number of hours or doses in study	345 (43.6%)	194 (20.0%)	539 (30.6%)	28 (8.8%)	133 (13.4%)	161 (12.3%)	95 (30.1%)
Hospital discharge	58 (7.3%)	27 (2.8%)	85 (4.8%)	21 (6.6%)	15 (1.5%)	36 (2.7%)	16 (5.1%)
No further need for parenteral opioid analgesia	149 (18.8%)	610 (62.8%)	759 (43.1%)	191 (59.7%)	721 (72.6%)	912 (69.5%)	0
Discontinued early	239 (30.2%)	141 (14.5%)	380 (21.6%)	80 (25.0%)	124 (12.5%)	204 (15.5%)	205 (64.9%)
Adverse event	35 (4.4%)	42 (4.3%)	77 (4.4%)	19 (5.9%)	68 (6.8%)	87 (6.6%)	8 (2.5%)
Inadequate analgesia	172 (21.7%)	77 (7.9%)	249 (14.1%)	33 (10.3%)	35 (3.5%)	68 (5.2%)	176 (55.7%)
Noncompliance / Protocol violation	6 (0.8%)	7 (0.7%)	13 (0.7%)	3 (0.9%)	9 (0.9%)	12 (0.9%)	1 (0.3%)
Suspected technical failure	3 (0.4%)	3 (0.3%)	6 (0.3%)	1 (0.3%)	0	1 (0.1%)	8 (2.5%)
Withdrawal of consent	14 (1.8%)	5 (0.5%)	19 (1.1%)	5 (1.6%)	5 (0.5%)	10 (0.8%)	6 (1.9%)
Other	9 (1.1%)	7 (0.7%)	16 (0.9%)	19 (5.9%)	7 (0.7%)	26 (2.0%)	6 (1.9%)

Abstracted from Sponsor's Table 1.1.6 page 188 to 190 of ISS.

7.1.3.2 Adverse events associated with dropouts

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			
	Original (n=791)	New (n=972)	Combined (n=1763)	Original (n=320)	New (n=993)	Combined (n=1313)	Placebo (n=316)
Adverse event	35 (4.4%)	42 (4.3%)	77 (4.4%)	19 (5.9%)	68 (6.8%)	87 (6.6%)	8 (2.5%)

Abstracted from Sponsor's Table 1.1.6 page 188 to 190 of ISS.

Table 7.1.3.2-1 Adverse Events Among Patients Discontinuing A Study Because Of An Adverse Event. (CAPSS-319-CAPSS-320 and FEN-PPA-401)

Body System	IONSYS N=42	IVPCA N=68
Respiratory	10(24)	14(21)
Cardiovascular	11(26)	19(28)
Skin	15(36)	9(21)

Digestive	30(71)	48(71)
Nervous	13(31)	25(37)

Data were abstracted from Sponsor's ISS. The number (percentage) of patients reporting an adverse event associated with the listed body system. The number of patient listed exceeds the total number of patients who withdrew from each treatment group because some patients reported more than a single adverse event. The overall frequency of dropouts associated with an adverse event was higher among the IV PCA treated patients compared to the IONSYS treated patients. When examined by body system, the frequency of dropouts associated with an adverse event was higher in the IONSYS treatment group only for adverse events associated with skin.

7.1.3.3 Other significant adverse events

Adverse events were typical for opioid use and sequelae of surgery.

7.1.4 Other Search Strategies

An evaluation of discontinuations and adverse event was performed on data from elderly patients in Studies CAPSS-319, CAPS-320 and FEN-PPA-401. The incidence of early discontinuations and adverse events among early discontinuations was similar for IONSYS and IV PCA. These findings are summarized in the tables below.

Elderly Patients (≥ 65 years old):

Table 7.1.4-1 Discontinuations Among the Elderly

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			
	Original (n=186)	New (n=313)	Combined (n=499)	Original (n=62)	New (n=320)	Combined (n=382)	Placebo (n=66)
Discontinued early	49 (26.3%)	37 (11.8%)	86 (17.2%)	14 (22.6%)	31 (9.7%)	45 (11.8%)	39 (59.1%)
Adverse event	8 (4.3%)	11 (3.5%)	19 (3.8%)	6 (9.7%)	17 (5.3%)	23 (6.0%)	3 (4.5%)
Inadequate analgesia	37 (19.9%)	22 (7.0%)	59 (11.8%)	5 (8.1%)	8 (2.5%)	13 (3.4%)	31 (47.0%)
Noncompliance / Protocol violation	2 (1.1%)	2 (0.6%)	4 (0.8%)	0	3 (0.9%)	3 (0.8%)	0

Abstracted from Sponsor's Table 2.1.6 from ISS.

Table 7.1.4-2 Adverse Event Incidence Among the Elderly

Study	E-TRANS® (fentanyl HCl) 25 µg	E-TRANS® (fentanyl HCl) 40 µg	E-TRANS® (fentanyl HCl) 25/40 µg	Placebo	IV PCA (morphine)	IM (morphine)
CAPSS-319	NA	73.6% (134/182)	NA	NA	77.9% (148/190)	NA
CAPSS-320	NA	69.6% (32/46)	NA	NA	76.1% (35/46)	NA
FEN-PPA-401	NA	64.7% (55/85)	NA	NA	64.3% (54/84)	NA

Note: The 25/40 µg treatment group is not present in this table, as no patients in pediatric study C2000005 could be ≥ 65 years.
Adverse events that occurred prior to study treatment are excluded from this table.
NA = Not applicable.

From Sponsor's Table 4.2.1 pages 3727 and 3728 of ISS

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

AEs were recorded at each assessment time or when otherwise volunteered by the patient. The severity and duration of the AE and its relationship to the study medication were recorded.

AEs were defined as unusual and most often undesirable symptoms or signs that occurred in study participants. These were to include clinically significant laboratory values and test results, concomitant illnesses, accidents, medical occurrences, or worsening of existing medical conditions that emerged during a study. Adverse events were to be collected beginning with initiation of study treatment (eg, application of IONSYS study treatments). Investigators were to assess the severity (mild, moderate, severe) and relationship (not related, possibly related, or probably related) of AEs to study drug and treated the patients as medically required until the AE either resolved or became medically stable. This treatment was to extend beyond the duration of the study. Treatments and medications required to treat AEs were to be recorded on the AE or Concomitant Medication CRF, per study protocol.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were generally categorized appropriately by body system using Costart terminology. Some skin reactions such as erythema were captured as nonroutine events in Study FEN-PPA-401. In this study, nonroutine events occurred in 51.1% of patients who received IONSYS (of which the largest portion were application-site reactions such as erythema/discoloration [37.2%], itching [7.1%], and edema [3.4%], and device malfunction or

failure [9.2%]) and in 17.9% of patients who received IV PCA morphine (of which the largest portion reflected problems with venous access and other unspecified events).

In Studies CAPSS-319 and CAPSS-320 nonroutine events related to pain management, reflected problems primarily attributed to the different modes of delivery, and occurred in similar proportions for IONSYS and IV PCA morphine treatments (range, 17.0%.22.3% of patients for both treatments).

7.1.5.3 Incidence of common adverse events

The most common adverse events were fever, nausea, vomiting and skin reactions. With the exception of severe skin reactions which were only reported in the IONSYS treated patients, the incidence of adverse events was similar between IONYSYS and IV PCA treatment groups. These data are summarized in the tables below.

7.1.5.4 Common adverse event tables

Table 7.1.5.4-1

Very Common Adverse Events (Incidence ≥10%)
(All Controlled Completed Studies)

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			
	Original (n=791)	New (n=972)	Combined (n=1763)	Original (n=320)	New (n=993)	Combined (n=1313)	Placebo (n=316)
Body as a Whole							
Fever	107 (13.5%)	171 (17.6%)	278 (15.8%)	65 (20.3%)	157 (15.8%)	222 (16.9%)	33 (10.4%)
Digestive System							
Nausea	324 (41.0%)	378 (38.9%)	702 (39.8%)	161 (50.3%)	423 (42.6%)	584 (44.5%)	69 (21.8%)
Vomiting	96 (12.1%)	130 (13.4%)	226 (12.8%)	34 (10.6%)	129 (13.0%)	163 (12.4%)	20 (6.3%)
Skin System							
Application site reaction-Erythema	74 (9.4%)	173 (17.8%)	247 (14.0%)	0	0	0	7 (2.2%)

Note: Adverse events are sorted by incidence across all treatment groups for each body system.
Adverse events that occurred prior to study treatment are excluded from this table.
This table includes the combined E-TRANS® subgroup with adverse events incidence >=10%.

Sponsor's Table 1.2.13 on page 486 of ISS

Table 7.1.5.4-2 Common Adverse Events

Common Adverse Events (Incidence 1% to <10%)
(All Controlled Completed Studies)

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			Placebo
	Original (n=791)	New (n=972)	Combined (n=1763)	Original (n=320)	New (n=993)	Combined (n=1313)	(n=316)
Body as a Whole							
Headache	88 (11.1%)	73 (7.5%)	161 (9.1%)	29 (9.1%)	48 (4.8%)	77 (5.9%)	21 (6.6%)
Abdominal pain	15 (1.9%)	21 (2.2%)	36 (2.0%)	12 (3.8%)	11 (1.1%)	23 (1.8%)	5 (1.6%)
Back pain	9 (1.1%)	20 (2.1%)	29 (1.6%)	4 (1.3%)	9 (0.9%)	13 (1.0%)	10 (3.2%)
Extremity pain	4 (0.5%)	14 (1.4%)	18 (1.0%)	4 (1.3%)	8 (0.8%)	12 (0.9%)	1 (0.3%)
Pain	7 (0.9%)	11 (1.1%)	18 (1.0%)	0	9 (0.9%)	9 (0.7%)	2 (0.6%)
Cardiovascular System							
Hypotension	18 (2.3%)	41 (4.2%)	59 (3.3%)	7 (2.2%)	65 (6.5%)	72 (5.5%)	2 (0.6%)
Tachycardia	10 (1.3%)	14 (1.4%)	24 (1.4%)	9 (2.8%)	28 (2.8%)	37 (2.8%)	1 (0.3%)
Hypertension	16 (2.0%)	13 (1.3%)	29 (1.6%)	3 (0.9%)	16 (1.6%)	19 (1.4%)	4 (1.3%)
Digestive System							
Constipation	19 (2.4%)	31 (3.2%)	50 (2.8%)	9 (2.8%)	22 (2.2%)	31 (2.4%)	2 (0.6%)
Flatulence	17 (2.1%)	14 (1.4%)	31 (1.8%)	8 (2.5%)	10 (1.0%)	18 (1.4%)	2 (0.6%)
Dyspepsia	10 (1.3%)	12 (1.2%)	22 (1.2%)	5 (1.6%)	8 (0.8%)	13 (1.0%)	1 (0.3%)
Ileus	10 (1.3%)	11 (1.1%)	21 (1.2%)	2 (0.6%)	8 (0.8%)	10 (0.8%)	1 (0.3%)
Hemic and Lymphatic System							
Anemia	29 (3.7%)	64 (6.6%)	93 (5.3%)	15 (4.7%)	72 (7.3%)	87 (6.6%)	2 (0.6%)
Metabolic and Nutritional System							
Hypokalemia	8 (1.0%)	14 (1.4%)	22 (1.2%)	2 (0.6%)	9 (0.9%)	11 (0.8%)	1 (0.3%)
Nervous System							
Dizziness	23 (2.9%)	53 (5.5%)	76 (4.3%)	13 (4.1%)	49 (4.9%)	62 (4.7%)	4 (1.3%)
Insomnia	20 (2.5%)	34 (3.5%)	54 (3.1%)	6 (1.9%)	27 (2.7%)	33 (2.5%)	16 (5.1%)
Anxiety	13 (1.6%)	17 (1.7%)	30 (1.7%)	11 (3.4%)	10 (1.0%)	21 (1.6%)	5 (1.6%)
Hypertonia	10 (1.3%)	18 (1.9%)	28 (1.6%)	4 (1.3%)	10 (1.0%)	14 (1.1%)	1 (0.3%)
Somnolence	14 (1.8%)	4 (0.4%)	18 (1.0%)	8 (2.5%)	16 (1.6%)	24 (1.8%)	0
Respiratory System							
Hypoxia	17 (2.1%)	30 (3.1%)	47 (2.7%)	11 (3.4%)	44 (4.4%)	55 (4.2%)	1 (0.3%)
Pharyngitis	12 (1.5%)	7 (0.7%)	19 (1.1%)	5 (1.6%)	19 (1.9%)	24 (1.8%)	5 (1.6%)
Skin System							
Pruritus	55 (7.0%)	45 (4.6%)	100 (5.7%)	40 (12.5%)	84 (8.5%)	124 (9.4%)	1 (0.3%)
Application site reaction-Itching	15 (1.9%)	40 (4.1%)	55 (3.1%)	0	0	0	2 (0.6%)
Application site reaction-Vesicles	8 (1.0%)	34 (3.5%)	42 (2.4%)	0	0	0	2 (0.6%)
Application site reaction-Other	8 (1.0%)	12 (1.2%)	20 (1.1%)	0	0	0	0
Application site reaction-Edema	2 (0.3%)	17 (1.7%)	19 (1.1%)	0	0	0	0
Urogenital System							
Urinary retention	19 (2.4%)	15 (1.5%)	34 (1.9%)	6 (1.9%)	29 (2.9%)	35 (2.7%)	2 (0.6%)

Sponsor's Table 1.2.13 on page 487-490 of ISS

Reviewer's comment: Application site reactions were exclusively represented in the IONSYS treatment group. This is expected because only IONSYS had direct contact with the skin. In contrast, pruritis was represented in the IV PCA treatment group because it is a systemic reaction to opioids.

Headache was more common in the IONSYS treatment group (n= 161, 9%) than among IV PCA treated patients (n=77, 6%) or placebo treated patients (n=21, 7%). The reason for this disparity is not known, but this reviewer speculates that fentanyl from IONSYS is unlikely to have directly caused headaches. Instead, it may be more likely that IV PCA morphine and rescue analgesics were more effective in treating headache pain that presented in the post-operative period than IONSYS.

7.1.5.5 Identifying common and drug-related adverse events

Rescue opioids in the first 3 hours
A specific feature of IONSYS identified in the prior NDA submission was that systemic fentanyl delivery was well below the nominal dose until about 3 hours after application of the product. This suggested that patients were unlikely to receive adequate analgesia from IONSYS in this time period and would therefore require rescue opioids for pain. It remained unclear that rescue dosing could be then managed safely because an uncertainty about the onset of fentanyl delivery by IONSYS had the potential to result in overdosing of opioid. The Sponsor provided new data that indicates similar cumulative dosing of rescue opioids in the first 3 hours after initiating IONSYS or IV PCA.

Table 7.1.5.5-1 Rescue Opioid Dosing During Hours 0-3

	CAPSS-319 Hip, n=799		CAPSS-320 Abdomen, n=504		FEN-PPA-401 Mixed, n=661	
Supplemental Opioid	E-TRANS® Fentanyl n=395	IV PCA Morphine n=404	E-TRANS® Fentanyl n=252	IV PCA Morphine n=254	E-TRANS® Fentanyl n=325	IV PCA Morphine n=335
No. Patients Used	67 (17%)	57 (14.1%)	52 (20.6%)	31 (12.2%)	36 (11.1%)	37 (11.0%)
Fentanyl Mean dose, mcg Range, mcg	(n=30) 105.7 10 – 400	(n=4) 93.8 25 – 200	(n=25) 61.9 12 –150	(n=2) 62.5 50 – 75	ND	ND
Morphine Mean dose, mg Range, mg	(n=42)* 7.4 2 – 24	(n=53) 5.4 2 – 19	(n = 29)* 5.2 1-12	(n= 31)* 5.9 1-15	(n=36) 7.5 1-25	(n=37) 6.5 1-30

Some patients in Studies CAPSS-319 (5), CAPSS-320 (5) received both fentanyl and morphine. Data were abstracted from Clinical Study reports CAPSS-319 (Tables 11.3.5-9 & 11.3.5-10), CAPSS-320 (Tables 11.3.5-9 & 11.3.5-10) and FEN-PPA-401 (Tables 11.3.5.8 & 11.3.5.9).

The pattern of adverse events that occurred in the first three hours was similar for each treatment arm as shown below.

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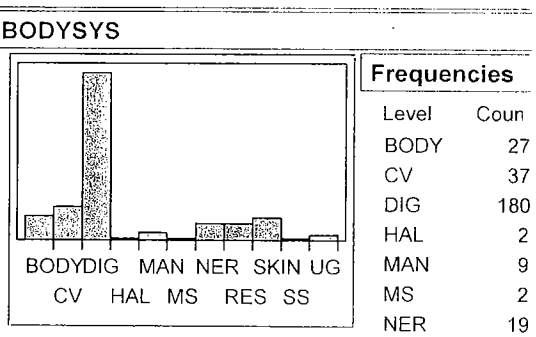
Figure 7.1.5.5-2 Distribution of Adverse Events by Body System

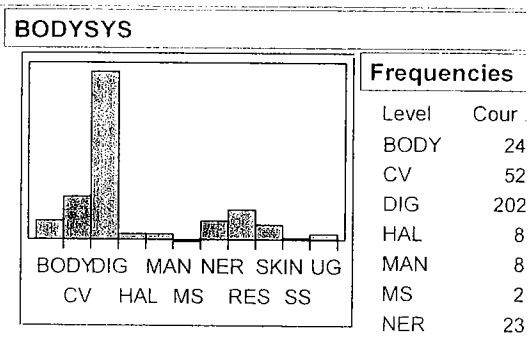
IONSYS



Frequencies

Level	Coun
BODY	27
CV	37
DIG	180
HAL	2
MAN	9
MS	2
NER	19
RES	18
SKIN	24
SS	3
UG	6
Total	327

IVPCA



Frequencies

Level	Cour
BODY	24
CV	52
DIG	202
HAL	8
MAN	8
MS	2
NER	23
RES	38
SKIN	19
SS	3
UG	7
Total	386

Findings were abstracted by this reviewer from ISS data tables for Studies 319, 320, 410. The displayed histogram is a graphical representation of "Frequencies", the number of AEs within the first 3 hours of product exposure. Body systems were identified by the Sponsor using CoStart terminology.

With the exception of adverse events related to skin, body-as-a-whole and metabolic and nutritional systems, IONSYS was associated with a lower or equal number and incidence of adverse events than IV PCA in the first 3 hours after initiating therapy.

7.1.5 Additional analyses and explorations

Adverse reactions of the skin described as blisters, burns, vesicles, rash or excoriations were reported in 43 patients (4%) out of 972 participating exposed to IONSYS in the new studies. Most skin reactions were mild or moderate in severity. Severe skin reactions were noted in 12 of patients out of 972 patients (1 %) participating in CAPSS-319, CAPSS-320 and Fen-PPA-401. The cumulative exposure was greater than 24 hours in all but two cases. Three severe injuries were described as "skin blisters" (patients CAPSS-320-1034 and CAPSS-320-34001) or "burnmark II grade" (patient FEN-PPA-401-10736) associated with the cathode, the anode or the adhesive of IONSYS.

Reviewer's comment: Blisters or vesicle formation can occur as a reaction to tape or other adhesive products such as EKG pads. The blistering associated with IONSYS is likely to be a localized allergic reaction rather than a thermal injury.

7.1.6 Less Common Adverse Events

Somnolence, confusion, hypoxia and hypoventilation were reported in < 3% of patient treated with IONSYS and were similar in incidence among patients treated with IV PCA in Studies CAPSS-319, CAPSS-320 and FEN-PPA-401.

7.1.7 Laboratory Findings

Clinical laboratory parameters were not assessed in the controlled, uncontrolled, or stopped studies. Standard laboratory assessments were conducted at the investigators. local laboratories in the pharmacology studies in healthy subjects, and the data are presented in the study reports. No clinically significant trends were identified in the evaluation of pre- and post study laboratory results.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the original controlled studies, respiratory function was the primary measure of systemic safety for the new controlled studies. Specifically, patients were monitored for respiratory depression and sedation. If the rate was less than 8 breaths per minute or excessive sedation was present, the patient was further evaluated. Other safety measures common to all controlled studies included systolic and diastolic blood pressure, heart rate, oxygen saturation, AEs, and topical events (reported as AEs). In addition, temperature was measured and a Ramsay Sedation Scale was completed in Studies CAPSS-319 and CAPSS-320. In Study FEN-PPA-401, the Glasgow Coma Scale was used to evaluate patients suspected of being overly sedated.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This review focused on the newly submitted active controlled studies CAPSS-319, CAPSS-320 and FEN-PPA-401 because instructional material for use of IONSYS had been modified following completion of the studies completed prior to the earlier NDA submission. Data from earlier studies were considered when there was sufficient similarity between the earlier and new studies. For example findings from Study 2007 were pooled with the newly submitted studies for comparative analysis of hypoxia associated with IONSYS vs. IV PCA because these studies share a similar design. A general comparison between findings between selected studies and the entire ISS was also performed when appropriate to evaluate consistency in clinical experience.

7.1.8.3 Standard analyses and explorations of vital signs data

In the controlled studies, the proportion of patients who had 2 or more consecutive vital signs out of normal range in the same direction was small and was similar for patients in the IONSYS and IV PCA morphine groups. Results for IONSYS in all clinical studies were similar to those for the controlled studies.

Oxygen saturation was specifically reviewed among vital sign measurements as a clinically significant marker for early toxicity associated with IONSYS. Among all controlled studies, the proportion of patients who had a minimum oxygen saturation value less than 90% (further separated into 88%-<90% and <88% in ISS) was small across all treatment groups but tended to be highest in the IV PCA morphine group: 4.2% (74/1763) for IONSYS, 6.5% (86/1313) for IV PCA morphine, and 0.9% (3/316) for placebo.

In all controlled studies, hypoxia was more frequently reported in patients who used rescue medication compared with those who did not use rescue medication in both the IONSYS (10.1% versus 1.9%) and IV PCA morphine (6.1% versus 3.8%) groups. This apparent increased incidence of hypoxia with rescue medication was not associated with concomitant increase in apnea or hypoventilation in IONSYS patients. In addition, the overall incidence of hypoxia in all controlled studies was no higher in the IONSYS group (2.7% [47/1763]) than in the IV PCA morphine group (4.2% [55/1313]).

Table 7.1.8.3-1 No Relationship Between Apnea or Hypoventilation and Hypoxia Reporting in Patients who Received Rescue Medication

	E-TRANS® (fentanyl HCl) 40 µg			IV PCA (morphine)			
	Original (n=289)	New (n=156)	Combined (n=444)	Original (n=87)	New (n=125)	Combined (n=212)	Placebo (n=178)
Respiratory System	22 (7.6%)	21 (13.5%)	43 (9.7%)	10 (11.5%)	17 (13.6%)	27 (12.7%)	1 (0.6%)
Hypoxia	8 (2.8%)	18 (11.6%)	26 (5.9%)	3 (3.4%)	10 (8.0%)	13 (6.1%)	1 (0.6%)
Hypoventilation	1 (0.3%)	0	1 (0.2%)	3 (3.4%)	3 (2.4%)	6 (2.8%)	0
Pharyngitis	2 (0.7%)	2 (1.3%)	4 (0.9%)	2 (2.3%)	1 (0.8%)	3 (1.4%)	0
Dyspnea	4 (1.4%)	0	4 (0.9%)	1 (1.1%)	0	1 (0.5%)	0
Apnea	2 (0.7%)	0	2 (0.5%)	1 (1.1%)	0	1 (0.5%)	1 (0.6%)
Lung disorder	1 (0.3%)	1 (0.6%)	2 (0.5%)	1 (1.1%)	1 (0.8%)	2 (0.9%)	0
Cough increased	2 (0.7%)	0	2 (0.5%)	1 (1.1%)	0	1 (0.5%)	0
Hiccup	1 (0.3%)	0	1 (0.2%)	0	2 (1.6%)	2 (0.9%)	0
Asthma	1 (0.3%)	0	1 (0.2%)	0	1 (0.8%)	1 (0.5%)	0
Rhinitis	2 (0.7%)	0	2 (0.5%)	0	0	0	0

Data were abstracted from Sponsor's ISS, Controlled completed Studies, Table 1.4.20-1 page 1362 of electronic table.

The increased incidence of hypoxia in the IONSYS group was analyzed by onset time of hypoxia to examine the temporal relationship between rescue medication use and hypoxia. Rescue medications were allowed only during the first 3 hours of the study, and thus the expected acute pharmacologic effect of the IV fentanyl or IV morphine rescue dose would be within the first 6 hours after treatment initiation. The majority of patients (30/43 patients in the IONSYS group and 32/55 in the IV PCA group) had hypoxia reported ≥ 6 hours after treatment initiation.

Table 7.1.8.3-2 Incidence and Timing of Hypoxia Associated with Use of Rescue Medication

Treatment	Rescue Med Use	Onset < 6 hours	Onset ≥ 6 hours	Overall
E-TRANS®	Used Rescue (n = 228)	6 (2.6%)	17 (7.5%)	23 (10.1%)
	Did Not Use Rescue (n = 1060)	7 (0.7%)	13 (1.2%)	20 (1.9%)
	Overall (n = 1288)	13 (1.0%)	30 (2.3%)	43 (3.3%)
IV PCA	Used Rescue (n = 212)	6 (2.8%)	7 (3.3%)	13 (6.1%)
	Did Not Use Rescue (n = 1101)	17 (1.5%)	25 (2.3%)	42 (3.8%)
	Overall (n = 1313)	23 (1.8%)	32 (2.4%)	55 (4.2%)

From Sponsor's Table 1.6.3, Tables 12.2.4.3 and 12.2.5.1-1 in the C-2000-007 Final Report, Tables 12.2.4.3 and 12.2.5.1-1a in the CAPSS-319 Final Report, Tables 12.2.4.3 and 12.2.5.1-1a in the CAPSS-320 Final Report, Appendixes 9.3.4.3 and 9.3.5.1 in the FEN-PPA-401 Final Report, and AP22CLIN\Work\iss2\stat\final\adhoc\HYPOXIAC.SAS

A disproportionate number of patients from a single site in Study CAPSS-319 (Site 19) had hypoxia (23 of the 46 patients enrolled at Site 19 reportedly had hypoxia). Upon further investigation by the Sponsor, it was determined that when a patient at this site was given routine supplemental oxygen, it was reported as an AE of oxygen desaturation, which was then encoded as hypoxia.

Reviewer's Comment: Based upon the timing of the reported events coded as hypoxia, the incidence of events related to rescue medication administered concomitantly with IONSYS appears similar to the incidence associated with rescue medication administered concomitantly with IV PCA morphine. Hypoxia resulting from opioids is expected to result from central depression of respiratory drive and would be associated with hypoventilation or apnea. These signs were not correlated among the adverse events reported. Bias in reporting oxygen administration as an adverse event despite this therapy as having been part of a hospital protocol may also have contributed to over-reporting of hypoxia. In summary, the incidence of hypoxia caused by rescue opioid therapy appears similar for IONSYS and IV PCA.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not assessed in the controlled, uncontrolled, or stopped studies. Electrocardiograms were performed as clinically indicated for screening and clinical management. No clinically significant trends in electrocardiograms were identified by the sponsor.

Reviewer's Comment: Fentanyl when rapidly administered intravenously in high doses can result in bradycardia. At the dosing and administration schedule of IONSYS, no effect on the electrocardiogram is expected.

7.1.10 Immunogenicity

No immunogenicity studies were performed.

7.1.11 Human Carcinogenicity

No Human Carcinogenicity studies were required because exposure to the product is very limited when used according to the proposed indication.

7.1.12 Special Safety Studies

An outstanding clinical concern indicated in the Division Approvable letter of July 23, 2004 was the complexity of the IONSYS system and the potential difficulty patients and caregivers might have in using it correctly. Two new sources of information were included in this submission to address this concern.

- Ease-of-Use Questionnaires were completed in the 3 new studies in their efficacy analysis of CAPSS319, CAPSS320 and FEN-PPA-401. Questionnaires were provided to patients, nurses, pharmacists and physical therapists. This review focused on the results of the nursing questionnaire because nurses are to be primarily responsible for application of IONSYS, estimation of the cumulative dose of fentanyl received by the patient and for disposal of the unused fentanyl.

- Study surveys were also conducted after completion of Studies CAPSS-319 and CAPSS-320 among patient and nurses to evaluate and improve instructional material.

Ease-Of-Use Questionaire: Nursing

Ease-of-Use responses may be an indicator of how well the instructions for use were understood because a system that may appear "time-consuming" or "bothersome" may not have been adequately explained in the instructions for use. The sponsor cited results from the nursing Ease-of Use Questionnaire to support their contention that prescription and administration of IONSYS was understood by nurses responsible for care of post-surgical patients. Their questionnaire consisted of 20 questions, answered categorically, that related to how time consuming or bothersome the system was to use. Specifically, the results of the overall mean (and median) of responses on the questionnaire indicate that IONSYS was more satisfactory to nurses because it was less time consuming or bothersome overall than IV PCA. In the table below, lower values indicate more satisfaction with the product.

Table 7.1.12-1 Overall Mean of Categorical Responses ± (SEM) from Ease-of-Use Nursing Questionnaire from CAPSS319, CAPSS-320 and FEN-PPA-401

Study	IONSYS	IV PCA
CAPSS-319	0.6 ± (0.04)	1.2 ± (0.05)

CAPSS-320	0.5 ± (0.04)	1.1 ± (0.05)
FEN-PPA-401	0.7 ± (0.04)	1.2 ± (0.05)

Data were abstracted from Sponsor's Table 11.2.7-11A on page 424 of Study Report of CAPSS-319, Sponsor's Table 11.2.7-5A on page 352 of Study Report of CAPSS-320 and Sponsor's Table 11.2.6.3-1 on page 182-4 of Study Report of FEN-PPA-401.

Reviewer's Comment: These findings support the Sponsor's conclusion that IONSYS was less bothersome or time consuming to nursing staff than IV PCA.

- ***Missing Data***

While overall measures of Ease-of -Use by the questionnaire suggested that IONSYS was more satisfactory than IV PCA, it is notable that there are more missing data from the IONSYS treatment arm than from the IV PCA arm in the reports from studies CAPSS 319 and CAPSS 320.

Table 7.1.12-2 Missing Responses from the Nursing Ease-of-Use Questionnaire Results from CAPSS319, CAPSS-320 and FEN-PPA-401

Study	IONSYS	IV PCA
CAPSS-319	74(20%) N=379	31(10%) N=325
CAPSS-320	50(22%) N=232	26(12%) N=221
FEN-PPA-401	3(1%) N= 238	2(1%) N= 215

Data were abstracted from Sponsor's Table 11.2.7-11A on page 424 of Study Report of Study CAPSS319, Sponsor's Table 11.2.7-5A on page 352 of Study Report of Study CAPSS320 and Sponsor's Table 11.2.6.3-1 on page 182-4 of Study Report of Study FEN-PPA-401.

Reviewer's Comment: The higher frequency of missing data in the IONSYS relative to the IV PCA treatment arm in two of the three studies suggests that the Sponsor's conclusion based upon an overall Ease-of-Use score could be biased.

- ***Estimation of the Administered Dose of Opioid***

Clinical data was collected that indirectly pertains to comprehension of the cumulative study drug dose administered to the patient. The IONSYS exhibits a code of light flashes to provide an estimate of the number of administered doses to the nurse. The Ease-of-Use questionnaire contained questions to evaluate how bothersome or time-consuming this code was to use. Either the patient's primary care nurse or a research nurse participating in the conduct of the study answered questions that evaluated ease of use in making determination about the amount of medication administered. The following tables indicate that someone other than a nurse was responsible for making a dose assessment for IONSYS more frequently than for IV PCA. This means that ease of use in determining the amount of medication could not be determined by the nurse completing the questionnaire.

Table 7.1.12-4 Study CAPSS319 Assessment of the amount of medication: Performed by Someone Other than a Nurse

Study CAPSS 319 Results of Nursing Ease-of-Use Questionnaire Questions 9, 19	IONSYS N=379	IV PCA N=325
Determination of Number of Doses Was Considered Time Consuming: Dose Assessment Was Performed by Someone Other Than a Nurse	102(27%)	41(13%)
Determination of Number of Doses Was Considered Bothersome: Dose Assessment Was Performed by Someone Other Than a Nurse	165(44%)	87(27%)

Data were abstracted from Sponsor's Table 11.2.7-15, CAPSS-319 Study Report pp 446 and 456. Questionnaire response in agreement with the preceding statement is listed in each row of the table as the number (percentage) of the total nurses who responded affirmatively to the statement.

Table 7.1.12-5 Study CAPSS320 Assessment of the amount of medication: Performed by Someone Other than a Nurse

Study CAPSS 320 Results of Nursing Ease-of-Use Questionnaire Questions 9, 19	IONSYS N=232	IV PCA N=221
Determination of Number of Doses Was Considered Time Consuming: Dose Assessment Was Performed by Someone Other Than a Nurse	64(28%)	35(16%)
Determination of Number of Doses Was Considered Bothersome: Dose Assessment Was Performed by Someone Other Than a Nurse	66(28%)	32(15%)

Data were abstracted from Sponsor's Table 11.2.7-9, CAPSS-320 Study Report pp 374 and 384.

Questionnaire response in agreement with the preceding statement is listed in each row of the table as the number (percentage) of the total nurses who responded affirmatively to the statement.

Table 7.1.12-8 Study FEN-PPA-401 Assessment of the amount of medication: Performed by Someone Other than a Nurse

Study FEN-PPA-410 Results of Nursing Ease-of-Use Questionnaire Questions 9, 19	IONSYS N=238	IV PCA N=215
Determination of Number of Doses Was Considered Time Consuming: Dose Assessment Was Performed by Someone Other Than a Nurse	69(29%)	60(28%)
Determination of Number of Doses Was Considered Bothersome: Dose Assessment Was Performed by Someone Other Than a Nurse	66(28%)	60(28%)

Data were abstracted from Sponsor's Table 11.2.6.3-4, FEN-PPA-401 Study Report pp. 542 and 552. Questionnaire response in agreement with the preceding statement is listed in each row of

the table as the number (and percentage) of the total number nurses who answered the questions (N).

Reviewer's Comment: Some nurses could not answer questions about how bothersome or time consuming it was to assess the delivered dose because they were not responsible for this task. The reported data from studies 319 and 320 are notable for a greater percentage of nurses reporting that they were Not Responsible for determining the amount of medication provided to the patient in the IONSYS treatment arm compared to the IV PCA arm. It seems possible that nurses who were not responsible for estimating the dose of medication were unable to perform this function, perhaps because the instructions were not clear.

The findings from Study 410 exhibited about the same percentage of nurses who were Not Responsible for estimating the amount of medication provided from IONSYS and IV PCA treatment. In this study, nurses were able to estimate IONSYS doses administered with about the same frequency as with currently available therapy. This suggests that in this study, the IONSYS instructional material was adequate to meet the requirements of the clinical environment.

- ***Disposal***

An element within the instructions for use is disposal of the used system. Disposal is particularly critical with IOSYS because the fentanyl reservoir is expected to contain a large amount of concentrated drug even after the device has completed its clinical life-span. Fentanyl in a high concentration may cause significant adverse events in health care workers who may inadvertently come in contact with the unused product. Furthermore, difficulty in disposal of IONSYS may illicit diversion more likely. Data describing ease of disposal were provided for the new studies in this submission (CAPSS319, CAPSS320 and FEN-PPA-410).

In particular the nursing Ease-of-Use Questionnaire assessed whether disposal of IONSYS was bothersome or time-consuming. The questionnaire was also used to indicate when someone other than the nurse disposed of unused drug from IONSYS or IV PCA. In the following summary data, the nurse completing the questionnaire was involved in either patient care or conduct of the research study.

Table 7.1.12-10 Study CAPSS 319 Disposal of the device: Performed by Someone Other than a Nurse

Study CAPSS 319 Results of Nursing Ease-of-Use Questionnaire Questions 10, 20	IONSYS N=379	IV PCA N=325
Assessment of Ease-of-Disposal Was Considered Time Consuming: Product Disposal Was Performed by Someone Other Than a Nurse	99(26%)	37(11%)
Assessment of Ease-of-Disposal Was Considered Bothersome: Product Disposal Was Performed by Someone Other Than a Nurse	164(43%)	85(26%)

Data were abstracted from Sponsor's Table 11.2.7-15, CAPSS-319 Study Report pp 447 and 457. Questionnaire response in agreement with the preceding statement is listed in each row of

the table as the number (and percentage) of the total number nurses who answered the questions (N).

Table 7.1.12-12 Study CAPSS 320 Disposal of the device: Performed by Someone Other than a Nurse

Study CAPSS 320 Results of Nursing Ease-of-Use Questionnaire Questions 10, 20	IONSYS N=232	IV PCA N=221
Assessment of Ease-of-Disposal Was Considered Time Consuming: Product Disposal Was Performed by Someone Other Than a Nurse	115(50%)	75(34%)
Assessment of Ease-of-Disposal Was Considered Bothersome: Product Disposal Was Performed by Someone Other Than a Nurse	112(48%)	71(32%)

Data were abstracted from Sponsor's Table 11.2.7-9, CAPSS-320 Study Report pp. 375 and 385. Questionnaire response in agreement with the preceding statement is listed in each row of the table as the number (and percentage) of the total number nurses who answered the questions (N).

Table 7.1.12-14 Study FEN-PPA-401 Disposal of the device: Performed by Someone Other than a Nurse

Study FEN-PPA-410 Results of Nursing Ease-of-Use Questionnaire Questions 10, 20	IONSYS N=238	IV PCA N=215
Assessment of Ease-of-Disposal Was Considered Time Consuming: Product Disposal Was Performed by Someone Other Than a Nurse	103(43%)	61(28%)
Assessment of Ease-of-Disposal Was Considered Bothersome: Product Disposal Was Performed by Someone Other Than a Nurse	104(44%)	61(28%)

Data were abstracted from Sponsor's Table 11.2.6.3-4, FEN-PPA-401 Study Report pp 553 and 543. Questionnaire response in agreement with the preceding statement is listed in each row of the table as the number (and percentage) of the total number nurses who answered the questions (N).

Reviewer's Comment: The reported data from studies 319, 320 and 401 are notable for a greater percentage of nurses reporting that they were Not Responsible for disposal of unused medication provided to the patient in the IONSYS treatment arm compared to the IV PCA arm. The Sponsor has indicated in subsequent communication that some of the nurses who were responsible for disposal may have been off duty at the time that the questionnaire was completed. While this is plausible, it does not explain why the percentage of nurses who did not perform disposal was higher in the IONSYS than in the IV PCA treatment arm. It seems equally plausible that nurses who were not responsible for disposal did not perform this duty because the instructions were not clear and they required someone else to assist them.

Nursing Survey Completed After Trials CAPSS-319 and CAPSS-320

The Nurse Survey evaluated nurses' knowledge and understanding of the appropriate and safe use of administering IONSYS after completion of Studies CAPSS-319 and CAPSS-320. Nurses from Study 401 did not participate. This survey was not part of the study protocols. Questions included identifying the appropriate IONSYS application site, concerns about touching the underside of the system, how to activate the system, how to determine if a dose is being delivered, how to determine when the system is ready to deliver another dose, the determination of the number of doses delivered, the meaning of LED blinking, and the need to instruct the patient to call for help if the system accidentally falls off. In the Nurse Survey in the US Studies CAPSS 319 & 320, nurses who had been exposed to at least one form of instructional material and had cared for at least one study patient were eligible to participate in the survey study.

There were 513 eligible nurses comprised of :

- 59 (11.5%) PACU Nurses
- 148 (28.8%) Clinical Study Nurses
- 259 (50.5 %) Floor nurses
- 47 (9.2%) Others

The sponsor reported that 90% or more of the responding nurses felt confident using IONSYS and that understanding of the system improved with experience using it to treat more patients.

Reviewer's comment: These findings represent a principal component of the Sponsor's response to provide clinical data regarding the adequacy of IONSYS teaching materials. It is notable that only about 60% of the respondents were nurses engaged in the routine medical care of the patients who were also treated with IONSYS.

The following examples are of summary data abstracted from the Sponsor's report.

Table 7.1.12-15 Understanding Delivery of Dose by Nurse Role

Item	PACU Nurse (N=42)	Clinical Study Nurse (N=141)	Floor Nurse (N=162)	Other (N=40)
15. How do you know a dose is being delivered? (A: The LED is lit continuously for 10 minutes; B: The LED is blinking; C: The system emits a continuous series of beeps) (Correct answer: A)				
A	31 (73.8%)	124 (87.9%)	100 (61.7%)	30 (75.0%)
B	6 (14.3%)	7 (5.0%)	32 (19.8%)	4 (10.0%)
C	2 (4.8%)	2 (1.4%)	9 (5.6%)	2 (5.0%)
Missing	3 (7.1%)	8 (5.7%)	21 (13.0%)	4 (10.0%)
16. How do you know when the system is ready to deliver another dose? (A: The LED is lit continuously for 10 minutes; B: The LED is blinking; C: The system emits a continuous series of beeps) (Correct answer: B)				
A	4 (9.5%)	1 (0.7%)	17 (10.5%)	0
B	34 (81.0%)	131 (92.9%)	115 (71.0%)	35 (87.5%)
C	1 (2.4%)	1 (0.7%)	3 (1.9%)	1 (2.5%)
Missing	3 (7.1%)	8 (5.7%)	27 (16.7%)	4 (10.0%)

Data were abstracted from table 7.2.2 Nursing Survey pg 608

Reviewer's comment: These data suggest that PACU nurses and Study nurses were better at understanding IONSYS functions than Floor nurses. This may reflect the higher level of experience PACU and Study nurses have with instrumentation. In clinical practice, floor nurses will be expected to manage IONSYS after a patient leaves PACU.

Table 7.1.12-16 Understanding Number of Doses by Nurse Role

Item	PACU Nurse (N=42)	Clinical Study Nurse (N=141)	Floor Nurse (N=162)	Other (N=40)
17. How can you determine the approximate number of doses delivered by the E-TRANS system? (A: Count the number of LED blinks; B: Count the number of beeps) (Correct answer: A)				
A	37 (88.1%)	133 (94.3%)	123 (75.9%)	36 (90.0%)
B	1 (2.4%)	0	12 (7.4%)	0
Missing	4 (9.5%)	8 (5.7%)	27 (16.7%)	4 (10.0%)
18. What dose range does each LED blink represent? (A: 1-3 doses; B: 1-5 doses; C: 10-20 doses) (Correct answer: B)				
A	4 (9.5%)	12 (8.5%)	24 (14.8%)	2 (5.0%)
B	33 (78.6%)	117 (83.0%)	106 (65.4%)	34 (85.0%)
C	0	0	1 (0.6%)	0
Missing	5 (11.9%)	12 (8.5%)	31 (19.1%)	4 (10.0%)

Data were abstracted from table 7.2.2 Nursing Survey pg 609

Reviewer's comment: These data suggest that PACU nurses and Study nurses were better at understanding IONSYS functions than Floor nurses. In clinical practice, floor nurses will be expected to manage IONSYS after a patient leaves PACU.

Table 7.1.12-17 Understanding Blinking Light and Loss of Adhesion by Nurse Role

Item	PACU Nurse (N=42)	Clinical Study Nurse (N=141)	Floor Nurse (N=162)	Other (N=40)
19. If the LED of the E-TRANS system is blinking 3 times, how many doses were delivered? (A: 3-5 doses; B: 11-15 doses: C: 30-40 doses) (Correct answer: B)				
A	6 (14.3%)	12 (8.5%)	29 (17.9%)	3 (7.5%)
B	31 (73.8%)	118 (83.7%)	105 (64.8%)	33 (82.5%)
C	0	0	1 (0.6%)	0
Missing	5 (11.9%)	11 (7.8%)	27 (16.7%)	4 (10.0%)
20. What do you tell a patient if the system accidentally falls off? (A: Tell the patient to put it back on; B: Tell the patient to call you immediately) (Correct answer: B)				
A	1 (2.4%)	2 (1.4%)	1 (0.6%)	0
B	39 (92.9%)	131 (92.9%)	144 (88.9%)	36 (90.0%)
Missing	2 (4.8%)	8 (5.7%)	17 (10.5%)	4 (10.0%)

Data were abstracted from table 7.2.2 Nursing Survey pg 610

Reviewer's comment: These data suggest that PACU nurses and Study nurses were better at understanding IONSYS functions than Floor nurses. In clinical practice, floor nurses will be expected to manage IONSYS after a patient leaves PACU.

Table 7.1.12-18 Understanding Dose Delivery by Number of IONSYS Patients Cared for by the Nurse

Item	Missing (N=12)	1-3 Patients (N=220)	4-6 Patients (N=77)	7-9 Patients (N=28)	>10 Patients (N=48)
15. How do you know a dose is being delivered? (A: The LED is lit continuously for 10 minutes; B: The LED is blinking; C: The system emits a continuous series of beeps) (Correct answer: A)					
A	11 (91.7%)	139 (63.2%)	64 (83.1%)	26 (92.9%)	45 (93.8%)
B	0	40 (18.2%)	7 (9.1%)	1 (3.6%)	1 (2.1%)
C	0	12 (5.5%)	2 (2.6%)	0	1 (2.1%)
Missing	1 (8.3%)	29 (13.2%)	4 (5.2%)	1 (3.6%)	1 (2.1%)
16. How do you know when the system is ready to deliver another dose? (A: The LED is lit continuously for 10 minutes; B: The LED is blinking; C: The system emits a continuous series of beeps) (Correct answer: B)					
A	0	18 (8.2%)	3 (3.9%)	1 (3.6%)	0
B	11 (91.7%)	162 (73.6%)	69 (89.6%)	26 (92.9%)	47 (97.9%)
C	0	5 (2.3%)	1 (1.3%)	0	0
Missing	1 (8.3%)	35 (15.9%)	4 (5.2%)	1 (3.6%)	1 (2.1%)

Data were abstracted from table 7.2.2 Nursing Survey pg 621

Reviewer's comment: These data suggest that nurses need to manage at least 7 to 9 patients with IONSYS in order to become an expert with the system.

Table 7.1.12-19 Understanding Number of Doses by Number of IONSYS Patients Cared for by the Nurse

Item	Missing (N=12)	1-3 Patients (N=220)	4-6 Patients (N=77)	7-9 Patients (N=28)	>10 Patients (N=48)
17. How can you determine the approximate number of doses delivered by the E-TRANS system? (A: Count the number of LED blinks; B: Count the number of beeps) (Correct answer: A)					
A	11 (91.7%)	175 (79.5%)	71 (92.2%)	25 (89.3%)	47 (97.9%)
B	0	10 (4.5%)	2 (2.6%)	1 (3.6%)	0
Missing	1 (8.3%)	35 (15.9%)	4 (5.2%)	2 (7.1%)	1 (2.1%)
18. What dose range does each LED blink represent? (A: 1-3 doses; B: 1-5 doses; C: 10-20 doses) (Correct answer: B)					
A	2 (16.7%)	29 (13.2%)	9 (11.7%)	1 (3.6%)	1 (2.1%)
B	9 (75.0%)	151 (68.6%)	61 (79.2%)	25 (89.3%)	44 (91.7%)
C	0	1 (0.5%)	0	0	0
Missing	1 (8.3%)	39 (17.7%)	7 (9.1%)	2 (7.1%)	3 (6.3%)

Data were abstracted from table 7.2.2 Nursing Survey pg 622

Reviewer's comment: These data suggest that nurses need to manage at least 7 to 9 patients with IONSYS in order to become an expert with the system.

Table 7.1.12-20 Understanding Blinking Light and Loss by Number of IONSYS Patients Cared for by the Nurse

Item	Missing (N=12)	1-3 Patients (N=220)	4-6 Patients (N=77)	7-9 Patients (N=28)	>10 Patients (N=48)
19. If the LED of the E-TRANS system is blinking 3 times, how many doses were delivered? (A: 3-5 doses; B: 11-15 doses; C: 30-40 doses) (Correct answer: B)					
A	2 (16.7%)	34 (15.5%)	12 (15.6%)	1 (3.6%)	1 (2.1%)
B	9 (75.0%)	148 (67.3%)	59 (76.6%)	25 (89.3%)	46 (95.8%)
C	0	1 (0.5%)	0	0	0
Missing	1 (8.3%)	37 (16.8%)	6 (7.8%)	2 (7.1%)	1 (2.1%)
20. What do you tell a patient if the system accidentally falls off? (A: Tell the patient to put it back on; B: Tell the patient to call you immediately) (Correct answer: B)					
A	0	4 (1.8%)	0	0	0
B	11 (91.7%)	192 (87.3%)	73 (94.8%)	27 (96.4%)	47 (97.9%)
Missing	1 (8.3%)	24 (10.9%)	4 (5.2%)	1 (3.6%)	1 (2.1%)

Data were abstracted from table 7.2.2 Nursing Survey pg 623

Reviewer's comment: These data suggest that nurses need to manage at least 7 to 9 patients with IONSYS in order to become an expert with the system.

Summary Reviewer's comment: These data indicate that the learning curve to use IONSYS is likely require experience with about 10 patients to understand the functions of the system and that floor nurses may require more assistance when using IONSYS than research or PACU nurses.

- ***Technical Failures in the Device***

The delivery of fentanyl is managed in-part by a lock-out system that is intended to prevent drug administration more frequently than of the minimum prescribed dosing interval of ten minutes. In the active-controlled studies, technical failures were suspected in 3.7% to 5.6% of IONSYS systems activated and 2.1% to 8.7% of the IV PCA pumps activated. The reasons for suspected technical failures of E-TRANS® fentanyl systems included —

Reviewer's Comment: Reliability of the lock-out and unit dose delivery features of IONSYS and the low rate of passive delivery of fentanyl are important features that contribute to patient safety of this system.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal symptoms are not anticipated with IONSYS because it is indicated only for acute post-operative pain.

The drug reservoir in an unused IONSYS contains 10,800 mcg of fentanyl. After an IONSYS unit has been used to its maximum capacity, 7,600 mcg of fentanyl remain in the drug reservoir. These are large quantities of fentanyl that may be readily extracted from the product and diverted for illegal use.

7.1.14 Human Reproduction and Pregnancy Data

An assessment of effect on reproduction and pregnancy in human beings was not performed.

7.1.15 Assessment of Effect on Growth

An assessment of effect on growth in human beings was not performed.

7.1.16 Overdose Experience

During Phase 3 trials for the original NDA, there were 2 cases of misuse that involved a family member pressing the dosing button. Improvements were subsequently made in the education of health care providers, patients, and family members for the 3 Phase 3b studies, and no additional cases of patient or family tampering occurred in these studies.

In the Phase 3B studies presented with this submission, there were no cases defined as simultaneous bradypnea less than 8 breaths per minute and excessive sedation although there was one case of subjective feelings of sedation.

7.1.17 Postmarketing Experience

IONSYS was approved for use in Europe on February 1, 2006. No post marketing data are available the time of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

A principal concern with the previous submission was that the product was complex to use and that the product instructions had not been adequately tested. A second concern was that the product was likely to require that rescue analgesics would be needed in the early treatment period and that ability to safely administer supplemental opioids had not been tested.

The 3 new studies were intended to evaluate the use of IONSY compared with morphine IV PCA in a typical clinical postoperative setting. Dosing of rescue opioids was to be in keeping with local customs and was not tightly controlled. For example, study protocols did not stipulate a specific dose of rescue opioid based upon the cumulative administered fentanyl by IONSYS (indicated by the number of light flashes). Only proposed product instructional material was to be used in the new studies to guide IONSYS administration.
The Ease-of-Use Questionnaire tools used to evaluate product instructions in the new studies indirectly assessed instructions for use by categorically measuring how time-consuming or bothersome were various aspects of clinical management with IONYS.

Deficiencies in the new studies are:

- Exclusion of patients with serious conditions that are a constant threat to life (ASA IV).
- Exclusion of patients with a Body Mass Index (BMI) > 40 kg/m^2
- Others than the patient care nurse may assess the administered dose of fentanyl by IONSYS and dispose of unused drug product.

Despite these limitations the new study reports and their data do provide adequate information about IONSYS, concomitant dosing of rescue opioid and the use of product instructional information to evaluate safety.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data used for this review is the data from 3 new active-controlled open label studies CAPSS-319, CAPSS-320 and FEN-PPA-410. There were 972 patients

exposed to IONSYS and 993 patients exposed to IV PCA in these studies. For some safety evaluations comparing INSYS to IV PCA, the data from the previously submitted active-controlled study C-2000-007 was included.

Table 7.2.1.1-1 Patient enumeration in Active Controlled Studies

	Multicenter active-controlled			
	C-2000-007	CAPSS-319	CAPSS-320	FEN-PPA-401
No. Patients Randomized and Treated				
Total	636	799	506	660
E-TRANS® fentanyl	316	395	252	325
IV PCA morphine	320	404	254	335
No. (%) Patients Discontinued in First 3 Hours				
Total	10 (1.6%)	13 (1.6%)	5 (1.0%)	4 (0.6%)
E-TRANS® fentanyl	6 (1.9%)	6 (1.5%)	2 (0.8%)	3 (0.9%)
IV PCA morphine	4 (1.3%)	7 (1.7%)	3 (1.2%)	1 (0.3%)
No. Evaluable Patients				
Total	626	786	501	656
E-TRANS® fentanyl	310	389	250	322
IV PCA morphine	316	397	251	334

From Sponsor's Summary Table E, Page 56.

Of the 2601 patients entering the active-controlled studies, 1288 received IONSYS and 1313 received IV PCA morphine. Of these, 1271 (98.7%) patients who received IONSYS and 1298 (98.9%) patients who received IV PCA morphine remained in the study for at least 3 hours after system application ie, beyond the period when supplemental IV opioid was available. For some analyses of the overall pattern of adverse events, the entire electronic data table was evaluated ISS. The ISS contained references to 2114 patients exposed to IONSYS (40 mcg fentanyl per dose) and 1354 patients exposed to IV PCA. Groups that were not evaluated for comparison in this review included patients receiving IONSYS placebo (device without fentanyl), IM morphine and E-Trans with 25 mcg of fentanyl.

7.2.1.2 Demographics

- Race

Table 7.2.1.2-1 Comparison of Exposure to IONSYS vs. IV PCA by Race in New Studies CAPSS-319, CAPSS-320, and FEN-PPA-401

	All Treatments	IONSYS	IV PCA
Caucasian	1739(88%)	857(44%)	882(45%)
Hispanic	41(2%)	18(1%)	23(1%)
Black	152(8%)	76(4%)	76(4%)
Asian	14(1%)	7(<1%)	7(<1%)

Other Race	19(1%)	14(1%)	5(<1%)
Total	1965(100%)	972(49%)	993(51%)

Data were abstracted from Sponsor's electronic data tables from individual studies.
Data are presented as number of patients (percent).

- Gender, Elderly Age Group and Concomitant Disease (ASA Classification)

Table 7.2.1.2-2 Comparison of Exposure to IONSYS vs. IV PCA by Gender, Elderly Age Group and Concomitant Disease in New Studies CAPSS-319, CAPSS-320, and FEN-PPA-401

Treatment	Males	Females	≥ 65 years old	≥ 75 years old	ASA 3
IONSYS	368(19%)	604(31%)	313(16%)	114(6%)	16(1%)
IV PCA	381(19%)	612(31%)	320(16%)	127(6%)	22(1%)
Totals	972(49%)	993(51%)	633(32%)	241(12%)	38(2%)

Data were abstracted from Sponsor's electronic data tables from individual studies.
Data are presented as number of patients (percent).

- Type of Surgery

Table 7.2.1.2-3 Comparison of Exposure to IONSYS vs. IV PCA by Type of Surgery in New Studies CAPSS-319, CAPSS-320, and FEN-PPA-401

Type of Surgery	All Treatments	IONSYS	IV PCA
Orthopedic	989(50%)	474(24%)	515(26%)
Lower abdominal	741(38%)	376(19%)	365(19%)
Upper abdominal	115(6%)	64(3%)	51(3%)
Other	120(6%)	58(3%)	62(3%)
Totals	1965(100%)	972(49%)	993(51%)

Data were abstracted from Sponsor's electronic data tables from individual studies.
Data are presented as number of patients (percent).

Reviewer's comment: The exposure of IONSYS was limited primarily to Caucasians, was among a disproportionately female population and contained too few patients with serious systemic disease (ASA 3) to evaluate. Other aspects of exposure by demographic group appeared to be generally representative of the post operative surgical population. The exposure of IONSYS to various demographic groups in all active controlled and placebo-controlled studies was similar to that of the new studies presented in the tables above.

7.2.1.3 Extent of exposure (dose/duration)

For the 1763 adult patients using IONSYS in the active and placebo-controlled studies, the duration of treatment was distributed as follows: 38 patients (2.2%) used the system for <3 hours, 759 (43.1%) for ≥3 to 24 hours, 561 (31.8%) for >24 to 48 hours, and 405 (23.0%) for >48 hours. The majority (56.5%) of patients used 11 to 50 doses total. All but 5 of the 1763 patients activated at least 1 dose from an IONSYS system. The estimated mean number of doses administered per patient was 29.0 for ≥3 to 24 hours (range, 0-93 doses), 45.0 for >24 to 48 hours (range, 0-163), and 68.4 for >48 hours (range, 13-218).

Similar to all patients in controlled studies, the majority of elderly patients (≥65 years old) in the controlled studies (62.1% [310/499]) used 11 to 50 doses total. However, the mean estimated number of doses was lower at each time point for elderly patients compared with all patients in the controlled studies (4.7 doses at <3 hours, 23.0 doses at ≥3 to 24 hours, 32.9 at >24 to 48 hours, and 58.8 doses at >48 hours). A similar pattern of dosing was seen in elderly patients (n=569) in all clinical studies. Dosing patterns for all patients (n=2114) and for elderly patients (n=569) in all clinical studies were similar to dosing patterns seen in the controlled studies.

Table 7.2.1.3-1 Number of Doses in Active-Controlled Studies IONSYS vs. IV PCA

Study Treatment	Time Point, n	Total No. of Doses Activated		Mean No. Doses Activated/Patient/ Hour (n)
		Mean (SEM)	Range	
E-TRANS® Fentanyl				
C-2000-007	24 hours, n=259	33.4 (1.22)	3–93	1.39 (n=259)
	Last dose, n=316	49.0 (2.15)	3–208	1.32 (n=316)
CAPSS-319	24 hours, n=395	30.6 (1.03)	0–93	1.36 (n=313)
	Last dose, n=394	44.5 (1.69)	0–208	1.27 (n=395)
CAPSS-320	24 hours, n=252	35.0 (1.22)	3–98	1.56 (n=194)
	Last dose, n=252	50.2 (2.20)	3–218	1.41 (n=252)
FEN-PPA-401	24 hours, n=307	24.5 (NR)	NR	1.02 (n=307)
	Last dose, n=325	46.2 (1.98)	0–168	0.91 (n=325)
IV PCA Morphine				
C-2000-007	24 hours, n=262	45.9 (1.66)	0–129	1.91 (n=262)
	Last dose, n=318	61.5 (2.63)	0–293	1.71 (n=318)
CAPSS-319	24 hours, n=403	36.8 (1.23)	0–142	1.65 (n=316)
	Last dose, n=404	47.5 (1.80)	0–215	1.43 (n=404)
CAPSS-320	24 hours, n=253	39.2 (1.56)	0–124	1.78 (n=192)
	Last dose, n=254	50.6 (2.47)	0–268	1.53 (n=254)
FEN-PPA-401	24 hours, n=314	34.5 (1.39)	0–145	1.44 (n=314)
	Last dose, n=335	54.7 (2.61)	0–278	1.17 (n=335)

NR=not reported

Source: C-2000-007, Tables 11.3.4-3, 11.3.4-4, 11.3.4-5, and 11.3.4-7; CAPSS-319, Tables 11.3.5-3A, 11.3.5-3B, 11.3.5-4A, 11.3.5-4B, and 11.3.5-5; CAPSS-320, Tables 11.3.5-3A, 11.3.5-3B, 11.3.5-4A, 11.3.5-4B, and 11.3.5-5; FEN-PPA-401, Tables 11.3.5.2, 11.3.5.3, 11.3.5.4a, 11.3.5.4b, and 11.3.5.6b.

The percentage of available doses activated was highest in the first hour after treatment initiation and ranged from 44.6% to 50.3% for IONSYS and from 29.6%.42.1% for IV PCA morphine. At the last dose administered, these percentages ranged from 15.0%.23.4% for IONSYS and from 11.8%.17.2% for IV PCA morphine. (Data source: Table 11.3.4-6 in the C-2000-007 report and Table 11.3.5-6 in each of the CAPSS-319, CAPSS-320, and FEN-PPA-401 reports.)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No other sources of data were used.

7.2.2.1 Other studies

No other studies were reviewed.

7.2.2.2 Postmarketing experience

IONSYS was recently approved for use in Europe, but there are no postmarketing data fro evaluation.

7.2.2.3 Literature

Published literature association with the use of IONSY was limited to summary data and did not provide additional information to the submission.

7.2.3 Adequacy of Overall Clinical Experience

The number of patients and their age range was sufficient for an assessment of safety with the use of IONSYS. Patients with severe medical conditions that are a constant threat to life were not evaluated.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

None was performed.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing met or exceeded the customary clinical standards for management of patients expected to be treated with IONSYS.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new pharmacokinetic studies were submitted.

An analysis of adverse events associated with IONSYS and concomitant medications with sedative properties was undertaken by the Sponsor (ISS Table 1.4.16 page 1239). Ninty-nine percent of patients received concomitant medication with sedative properties. These medications included other opiates, sedative hypnotics, tranquilizers, antihistamines and phenothiazines. No patient treated with IONSYS experienced severe respiratory depression and the incidence of adverse events or changes in vitals signs that identify respiratory depression was comparable in the IONSYS and the IV PCA treatment groups.

A review of the ISS for patients treated with IONSYS who received CYP3A4 inhibitors (96% of patients) or inducers (26% of patients) of fentanyl metabolism was also performed by the Sponsor (ISS Table 1.4.16 page 1240-1335). In the subset of patients who received inhibitors and in the subset of patients who received inducers, there were no substantial differences in the incidence of nausea, vomiting, headache, pruritus, apnea, hypoxia, hypoventilation, somnolence or confusion relative to all patients treated with IONSYS.

Patients in Study CAPSS-319 were treated with refecoxib (Vioxx) until it was discontinued. The incidence of treatment-related adverse events was not affected by concomitant refocoxib therapy.

Reviewer's comment: The Sponsor's evaluation of metabolism, clearance and interaction of IONSYS with other medication appears adequate. No new safety signals were developed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events associated with similar products are expected to be captured adequately by the CRFs. No further studies are recommended at this time.

7.2.8 Assessment of Quality and Completeness of Data

The submitted data appeared to be generally complete and of sufficient quality for review.

7.2.9 Additional Submissions, Including Safety Update

No safety update was submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

- The safety of IONSYS was comparable to IV PCA except for application site skin reactions. Serious skin adverse events were only reported among the IONSYS patients. The most severe skin reactions associated with IONSYS included blistering.

- There was no evidence that dosing rescue opioids for patients treated with IONSYS resulted in respiratory depression despite imprecision in the IONSYS display of the number of fentanyl doses administered.

- Elderly patients were not at increased risk of serious adverse events when treated with IONSYS compared to IV PCA.

- The data were limited by exclusion of ASA 4 patients and an enrollment of ASA 3 patients that was too small to enable a safety analysis.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data was generally pooled among the newly submitted studies CAPSS-319, CAPSS-320 and FEN-PPA-401. Comparisons were made on a case by case basis for certain safety findings with the previously submitted active-controlled study C-2000-007 and with the entire ISS database.

7.4.1.1 Pooled data vs. individual study data

The new studies presented in this submission are similar in patient population, surgical procedure and methodology so the safety data from these studies was combined for analysis.

The sponsor included the results from the previously submitted active-controlled Study C-2007 with the results from CAPSS-319, CAPSS-320 and FEN-PPA-401 in many of their analyses. These findings are incorporated into this review when the results of all the active controlled studies are similar to the results from the new active-controlled studies.

Data from individual studies CAPSS-319, CAPSS-320 and FEN-PPA-401 were evaluated separately and in aggregate for analysis of demographics of the study populations and when evaluating dropouts to detect possible bias related to differences in recruitment.

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Vital signs values that indicated clinically relevant respiratory depression (respiratory rate <8 breaths/minute and oxygen saturation <90%) and AE data were analyzed to compare high-frequency IONSYS users (>60 doses in the first 24 hours) and low-frequency users (≤60 doses). This analysis was conducted for patients in the controlled studies and in all clinical studies.

In the controlled studies, a higher proportion of patients who used >60 doses (13 or more displayed flashes) in the first 24 hours reported AEs compared with those who used ≤60 doses (82.7% [134/162] versus 72.2% [1156/1601]). The most frequently reported AEs in patients who used >60 doses in 24 hours and those who used ≤60 doses were nausea (45.7% versus 39.2%), fever (22.8% versus 15.1%), headache (18.5% versus 8.2%), vomiting (15.4% versus 12.6%), application site reaction-erythema (14.2% versus 14.0%), and pruritus (13.6% versus 4.9%). Other AEs reported by >5% of patients

who used >60 doses in 24 hours compared with those using ≤60 doses were hypoxia (8.6% versus 2.1%), dizziness (7.4% versus 4.0%), and insomnia (6.2% versus 2.7%). Of the 7 patients in a new controlled study who had a treatment-related SAE, none used >60 doses within the first 24 hours. Of the 4 patients in the original controlled studies who had a treatment-related SAE, 2 (1 had confusion and 1 had nausea and vomiting) used >60 doses, and 2 (both had ileus) used 58 doses each. None of these related SAEs were opioid-related respiratory events.

7.4.2.2 Explorations for time dependency for adverse findings

The pattern of adverse events in the first 3 hours after administration was reviewed by body system in section 7.1.5. It is in this early treatment interval that uncertainty about the cumulative dose of opioid would be expected to complicate management of patients treated with IONSYS. The pattern and number of adverse events was similar for IONSYS and IV PCA in this time period in populations that were comparable in size, demographic markers and medical condition.

An analysis of adverse events over 24 hours associated with the cumulative dose of opioid administered from IONSYS was also performed. The cumulative number of doses is correlated with the time of exposure, but cumulative dose is felt to be more relevant clinically than time *per se* because rate of passive transfer of fentanyl from IONSYS is low.

7.4.2.3 Explorations for drug-demographic interactions

- ***Race***

In the controlled studies, a similar percentage of Caucasian and Black patients reported at least 1 AE with IONSYS use. The proportion of patients in the controlled studies who reported at least 1 AE using IONSYS was 73.1% (1084/1482) for Caucasians, 71.3% (122/171) for Blacks, and 76.4% (84/110) for other races which included Asian, Hispanic, Polynesian, and all others. There are no further comparisons with races other than Blacks and Caucasians because the studied population is heterogeneous and comprises a small number of patients. The most frequently reported AEs (≥5% of patients overall) in patients using IONSYS are summarized in Table 7.2.1.2-1. In the controlled studies, the proportions of Caucasian patients and Black patients reporting AEs of fever, pruritus, and anemia were similar; whereas the following AEs were reported by a higher proportion of Caucasian patients than Black patients: nausea (40.5% versus 34.5%), Application Site Reactions) ASR-erythema (14.5% versus 5.8%), vomiting (13.0% versus 8.8%), and headache (9.5% versus 5.8%). The lesser frequency of ASR-erythema in Blacks may be due to the greater difficulty in detecting redness on darker pigmented skin. The results for all clinical studies were similar, except that fever was reported by a higher proportion of Caucasian versus Black patients (17.4% versus 15.1%).

Reviewer's Comment: This trend in ASR related to skin pigmentation was also noted in the clinical review of the previous NDA submission by Dr. Elizabeth McNeil.

Table 7.4.2.3-1 Adverse Events with an Incidence of ≥ 5%, Compared by Race

Adverse Event	Number (%) of Patients	
	Caucasians	Blacks
Controlled Studies (n)	1482	171
Nausea	600 (40.5%)	59 (34.5%)
Fever	229 (15.5%)	27 (15.8%)
ASR-Erythema	215 (14.5%)	10 (5.8%)
Vomiting	193 (13.0%)	15 (8.8%)
Headache	141 (9.5%)	10 (5.8%)
Pruritus	83 (5.6%)	8 (4.7%)
Anemia	76 (5.1%)	9 (5.3%)

Note: Adverse events included if incidence is ≥ 5% in patients overall. Source: Table 1.4.4 of ISS, All Controlled Studies

- *Gender*

The patient population in controlled studies was primarily female (66.6% [1174/1763]). In patients using IONSYS, more females than males reported at least 1 AE in the controlled studies (75.7% [889/1174] versus 68.1% [401/589]). Nausea, which was also the most frequently reported AE, was reported at a lower incidence in males than females. For the other frequently reported AEs (≥5% of patients overall), all except for fever and ASR-erythema were reported at a higher incidence in females than males using IONSYS. Results in all clinical studies were similar to those of the controlled studies.

- *Age*

No overall differences were observed in the safety of IONSYS in elderly patients (≥65 years including a subpopulation ≥75 years) and adult patients for all controlled studies. Similar findings were reported by the Sponsor for all clinical studies.

Table 7.4.2.3-2 Adverse Events with an Incidence of ≥ 5%, Compared by Age

Adverse Event	Number (%) of Patients		
	18 – 64 years	65 – 90 years	75 – 90 years[a]
Controlled Studies (n)	1264	499	174
Nausea	544 (43.0%)	158 (31.7%)	48 (27.6%)
Fever	201 (15.9%)	77 (15.4%)	20 (11.5%)
Anemia	45 (3.6%)	48 (9.6%)	20 (11.5%)
Vomiting	179 (14.2%)	47 (9.4%)	14 (8.0%)
ASR-Erythema	213 (16.9%)	34 (6.8%)	5 (2.9%)

Note: Adverse events included if incidence is ≥ 5% in the elderly (≥ 65 years). Patients 75-90 years old are a subgroup of those 65-90 years old. Source: Tables 1.4.2 of ISS, All Controlled Studies

The incidence of the following events was slightly higher (≥1%) in patients ≥65 years compared with patients who were 18 to 64 years of age: hypotension (4.4% versus 2.9%), confusion (1.8% versus 0.2%), hypokalemia (2.6% versus 0.7%), hypoxia (3.4% versus 2.4%), and hypoventilation (1.6% versus 0.2%). Conversely, the following events were slightly lower (≥1%) in patients ≥65 years compared with those 18 to 64 years of age: dizziness (2.4% versus 5.1%), pruritus (2.4% versus 7.0%), application site itching (1.4% versus 3.8%), and application site vesicles (0.2% versus 3.2%). (In patients on IV PCA morphine, the incidence of hypotension, confusion, and hypoxia was also increased in patients ≥65 years compared with those 18 to 64 years [hypotension 7.9% versus 4.5%; confusion 3.9% versus 0; hypoxia 5.8% versus 3.5%]). IONSYS was also well tolerated in 174 patients in the controlled studies who were ≥75 years old. A smaller percentage of patients ≥75 years reported at least one AE (66.1%, 115/174) compared with patients 18-64 years (74.5% [942/1264]). With the exception of anemia, the most frequently reported AEs (nausea, fever, vomiting, and ASR-erythema) were reported less frequently in patients ≥75 years compared with those 18 to 64 years and those ≥65 years.

- ***Type of Surgery***

AEs are tabulated by treatment group for orthopedic, upper abdominal, thoracic/chest, lower abdominal and other surgeries. This review focused on orthopedic, upper abdominal, and lower abdominal surgeries because fewer than 5% of patients using IONSYS were in either of the other surgery type subgroups (thoracic/chest and other). A higher proportion of patients with upper abdominal surgery reported at least 1 AE compared with patients who had lower abdominal or orthopedic bone surgery in the controlled studies (80.4% [78/97] versus 75.9% [615/810] and 68.9% [533/774], respectively).

Table 7.4.2.3-3 Adverse Events with an Incidence of ≥ 5%, Compared by Age

Adverse Event	Number (%) of Patients		
	Orthopedic Bone	Upper Abdominal	Lower Abdominal
Controlled Studies (n)	774	97	810
Nausea	243 (31.4%)	43 (44.3%)	382 (47.2%)
Fever	171 (22.1%)	11 (11.3%)	93 (11.5%)
ASR-Erythema	69 (8.9%)	26 (26.8%)	125 (15.4%)
Vomiting	89 (11.5%)	11 (11.3%)	108 (13.3%)
Headache	45 (5.8%)	13 (13.4%)	92 (11.4%)
Pruritus	31 (4.0%)	4 (4.1%)	61 (7.5%)
Anemia	68 (8.8%)	0	24 (3.0%)

Note: Adverse events included if incidence is ≥5% in patients overall.
Source: Table 1.4.5

Note: Adverse events included if incidence is ≥ 5% in patients overall. Source: Table 1.4.5

Reviewers' Comment: Upper abdominal surgery is associated with increased risk of systemic morbidity than lower abdominal surgery or orthopedic surgery because of increased likelihood of traumatic disturbance of diaphragmatic function with upper abdominal surgery.

Nausea and headache were reported by a higher proportion of patients who had abdominal surgery compared with those who had orthopedic surgery (Table). Conversely, fever and anemia were reported by a higher proportion of patients who had orthopedic bone surgery compared with those who had upper or lower abdominal surgery. Application site reactions (erythema) varied across the 3 surgery categories, with upper abdominal having the highest incidence of the 3 categories (possibly an artifact of the small number of patients in the upper abdominal group) and orthopedic bone having the lowest incidence. Results in all clinical studies were similar to those in the controlled studies.

7.4.2.4 Explorations for drug-disease interactions

No specific analysis of drug-disease interaction was performed. The American Association of Anesthesiology classification scheme can be used to indicate the severity of underlying medical conditions, but the most patients were listed as ASA 1 or 2, i.e. having mild or moderate disease so analysis by ASA category was not performed.

7.4.2.5 Explorations for drug-drug interactions

No formal drug interaction studies were conducted by the Sponsor for IONSYS.

Use of supplemental IV opioids and non-opioid adjunctive medications such as Vioxx and COX-2 inhibitors was examined.

To assess the possible effects of concomitant use of drugs that are CYP3A4 inhibitors or inducers of fentanyl metabolism, data from the 1763 adult patients who received IONSYS in the completed controlled studies were examined to identify the patients using such medications.

The database was also searched for adult patients using IONSYS in the controlled studies who received potentially sedating concomitant medications.

7.4.3 Causality Determination

Causality between respiratory adverse events and use of IONSY was a specific focus of this review because opioid administration is associated with depression of respiratory drive by the central nervous system. Post operative patients are at particular risk of impaired respiratory gas exchange because of concomitant inhibition of hypoxic mediated pulmonary vasoconstriction. atelectasis associated with mechanical ventilation and dependency, respiratory muscle weakness

from residual neuromuscular blockade, splinting and hypoventilation from wound pain and other common sequelae of surgery. Any of these factors can result in hypoxemia, but in association with a depression of respiratory drive patient management becomes more complicated.

IONSYS was not associated with hypoventilation or apnea more frequently than was IV PCA. Serious adverse events identified as hypoxia in patients treated with IONSYS were not associated with signs of centrally mediate respiratory depression as would be expected from an over dose of opioids.

Skin reactions caused by IONSYS were localized to the application site and were presumed to be caused by the product.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The maximum dosing regimen enables patients to self administer 40 mcg of fentanyl at maximum hourly rate of 240 mcg with a maximum dose of 3200 mcg per device. At the maximum rate of administration a single device would be able to deliver a dose every 10 minutes for 13 hours and 20 minutes. In practice, a device was seldom replaced on a patient in less than 24 hours and the utilization of the available doses per device (typically 40-50 doses/24 hours) was much less than the maximum allowed by the system. This dose of fentanyl is not excessive for ongoing analgesic requirements following major surgery.

8.2 Drug-Drug Interactions

No specific Drug-Drug Interactions studies were conducted.

However, a specific clinical concern indicated in the Division Approvable Letter of July 23, 2004 was that dosing opioids concomitantly with IONSYS would be problematic. The basis of this concern is that during the first three hours of IONSYS treatment systemic fentanyl was not detectable so that IONSYS was not expected to be efficacious in this early post operative period. Furthermore uncertainty associated with the timing of onset of IONSYS efficacy could theoretically result in an opioid overdose if rescue opioids were given in this early postoperative period. The Sponsor was advised to provide:

Clinical data evaluating conversion from and adjunctive therapy with other opioid analgesics during the early treatment phase with IONSYS system.

The Sponsor's new clinical studies were examined independently for the percentage of patients requiring rescue and the cumulative opioid dose administered in the first 3 hours of treatment with either IONSYS or IV PCA.

Amount of Rescue Medication prescribed in the first 3 Hours: CAPSS319

Rescue Medication	E-TRANS (fentanyl) 40 µg (N=389)	IV PCA morphine (N=397)
Fentanyl (µg)		
n	29 (7.5%)	4 (1.0%)
Mean (SEM)	95.5 (14.71)	93.8 (38.70)
Median	50.0	75.0
Range	10 to 300	25 to 200
Morphine (mg)		
n	40 (10.3%)	53 (13.4%)
Mean (SEM)	7.2 (0.81)	5.4 (0.53)
Median	5.0	4.0
Range	2 to 24	2 to 19

Abstracted from Sponsor's Table 11.2.5-10 on page 351, Study Report CAPSS319

About 18% of the IONSYS patients compared to about 14 % of the IV PCA patients in Study 319 required rescue opioids. The cumulative dose of rescue opioid in each treatment group is similar from a clinical perspective.

Amount of Rescue Medication prescribed in the first 3 Hours: CAPSS320

Rescue Medication	E-TRANS (fentanyl) 40 µg (N=252)	IV PCA morphine (N=254)
Fentanyl (µg)		
n	25 (9.9%)	2 (0.8%)
Mean (SEM)	61.90 (8.240)	62.50 (12.500)
Median	50.00	62.50
Range	12.5 to 150.0	50.0 to 75.0
Morphine (mg)		
n	29 (11.5%)	31 (12.2%)
Mean (SEM)	5.24 (0.627)	5.87 (0.721)
Median	4.00	5.00
Range	1.0 to 12.0	1.0 to 15.0

Abstracted from Sponsor's Table 11.3.5-10 on page 483. Study Report CAPSS320

About 21% of the IONSYS patients compared to about 13 % of the IV PCA patients in Study 320 required rescue opioids. The cumulative dose of rescue opioid in each treatment group is similar from a clinical perspective.

Amount of Rescue Medication prescribed in the first 3 Hours: FEN-PPA-401

	E-TRANS® fentanyl PCA	IV morphine PCA
Evaluable Patients		
N	322	334
Did require rescue medication n (%)	36 (11.2%)	37 (11.1%)
ITT Patients		
N	325	335
Did require rescue medication n (%)	36 (11.1%)	37 (11.0%)
Morphine (mg)		
Mean (SEM)	7.5 (1.08)	6.5 (1.03)
Range	1-25	1-30
Median	5.0	5.0

Abstracted from Sponsor's Table 22 and 23 on page 87, Study Report FEN-PPA-401

About 11% of the IONSYS patients and IV PCA patients in Study 401 required rescue opioids. The cumulative dose of rescue opioid in each treatment group is also very similar from a clinical perspective.

Reviewer's comment: The mean (or median) and range of cumulative rescue opioids in patients receiving IONSYS is not extraordinary. The mean (or median) dose is somewhat higher than with IV PCA, but not so high that it would be difficult to manage in the typical postoperative setting. Additional support for the practicality of managing rescue opioid during IONSYS treatment comes from the distribution of data regarding the cumulative rescue dose. The mean is only slightly higher than the median of cumulative rescue dose. This modest level of skewness in the distribution function indicates that nearly as many patients require little rescue medication as require higher doses among the patients who do need additional analgesia. Finally, the percentage of patients requiring rescue, while somewhat higher in the IONSYS treatment arm compared to IV PCA, it does not suggest that the frequency with which rescue analgesia will be needed is clinically unmanageable

8.3 Special Populations

There is adequate representation of the elderly population in the safety database. Adverse event are more frequent in the elderly patient who participated with about equal frequency in the IV PCA and IONSYS treatment arms.

8.4 Pediatrics

Only preliminary work has been conducted in the pediatric population. Trials are required to demonstrate efficacy in post-surgical pediatric patients between 6 and 18 years old.

8.5 Advisory Committee Meeting

Phase 3 trial designs were presented to the advisory committee in 1996.

8.6 Literature Review

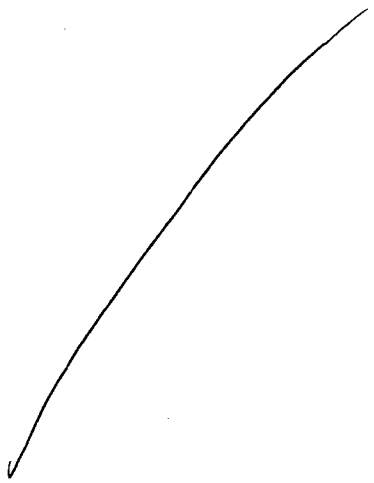
The risks associated with the clinical use of IV PCA have been reviewed by the Department of Veterans Affairs (VA) National Center for Patient Safety using Hazard Analysis and Critical Control Point (HACCP) methodology originally developed by FDA (http://www.patientsafety.gov/SafetyTopics/HFMEA/HFMEA_JQI.pdf. and http://www.hospitalconnect.com/medpathways/tools/content/2_A.pdf, accessed 5/05/06).

This hazard analysis was used as a benchmark when considering the risks and benefits of IONSYS.

8.7 Postmarketing Risk Management Plan

The risks addressed by the sponsor for this product are overdose, underdose, accidental exposure, abuse, mechanical failures, use in patients with a history of drug abuse, and leaving the medically supervised setting.

The Sponsor's risk management plan consists of



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- § 552(b)(4) Trade Secret / Confidential
- § 552(b)(5) Deliberative Process
- § 552(b)(4) Draft Labeling

9 OVERALL ASSESSMENT

9.1 Conclusions

IONSYS is therapeutically safe for the proposed indication in a well-controlled and carefully monitored post operative environment where opioids can be titrated safely and when the caregivers clearly understand how the product is to be used. The new studies provided by the Sponsor generally support, but did not fully elucidate whether staff patient care nurses are able to determine the number of administered doses of fentanyl by IONSYS or dispose of the unused fentanyl. The data collected from the nursing Ease-of-Use Questionnaire indicated that research or study coordinator nurses were responsible for evaluation of the IONYS in about 40% of the cases. Furthermore, someone else other than a nurse (staff nurse, research nurse or nurse study coordinator) was responsible for determining the number of doses administered or disposing of unused drug for IONSYS disproportionately when compared with IV PCA. These results complicate a determination of whether the instructional material to be used by nurse care-givers was adequate. A post-studies Nursing Survey support the conclusion that the respondent nurses were generally comfortable using IONSYS and were able to assess the internal dosing monitor provided that they had cared for about 10 patient treated with the device.

The clinical significance of a failure to accurately estimate the number of doses of fentanyl delivered by IONSYS to an individual patient is expected to be minimal because doing orders for rescue opioids are based primarily on the patient's current state of pain and general physical condition rather than the total cumulative dose. In the new study reports, the regimen for rescue opioids was not stipulated by the study protocols, but instead was practiced according to local institutional standards.

Failure to dispose of unused fentanyl in IONSYS is of more concern because of the high risk for diversion and abuse. It remains unclear that the nurses participating were comfortable with disposal because a disproportionate percentage of nurses completing the Ease-of-Use Questionaire for IONSYS indicated that this task was performed by someone else as compared to the IV PCA arm. Also, practicality the proposed plan to dispose of unused fentanyl by flushing the plastic IONSYS drug reservoir has not been evaluated.

9.2 Recommendation on Regulatory Action

IONSYS may be approvable based upon a finding of efficacy from study reports filled in the previous submission and a finding of safety for patients treated with the product supported by data included with the current submission. Training of nurses who will use IONSYS is likely to require careful supervision in the post marketing period with possible additional revisions to instructional material. Disposal of remaining fentanyl in the drug reservoir may constitute a risk to the public health unless feasibility of the proposed method of disposal can be assured.

9.3 Recommendation on Postmarketing Actions

The Sponsor should perform post-marketing nursing survey on instructional material especially with regard to estimation of cumulative fentanyl administered by IONSYS to determine whether product labeling may be improved.

9.3.1 Risk Management Activity

The sponsor should evaluate the method of disposal of the IONSYS drug reservoir and report the findings.

9.3.2 Required Phase 4 Commitments

Trials are required to demonstrate efficacy in post-surgical pediatric patients between 6 and 18 years old.

9.3.3 Other Phase 4 Requests

IONSYS may have therapeutic benefits to patients treated in ambulatory care centers. Further study in this patient population may be recommended.

9.4 Labeling Review

The principal clinical changes to the Sponsor's proposed label were:

- to edit the Boxed Warning;
- to delete the [redacted]
- to replace [redacted]

10 APPENDICES

10.1 Review of Individual Study Reports (New Studies in this Submission)

10.1.1 Protocol: CAPSS-319

Title: Comparison of the Safety and Efficacy of Patient Controlled Analgesia Delivered by Fentanyl HCl Transdermal System Versus Morphine IV Pump for Pain Management after Primary Unilateral Total Hip Replacement

Objective:
The primary objective of this study was to compare the safety and efficacy of IONSYS treatment versus IV PCA morphine treatment for the management of post-operative pain in patients who had undergone primary unilateral total hip replacement.

Study Design: multicenter, open-label, randomized, comparative, parallel treatment study.

Study medication, dose schedule, and mode of administration:

Test Product
Patients randomized to IONSYS received 40 micrograms (mcg) fentanyl per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 mcg/hour) or a maximum of 80 doses (3.2 mg) with each device.

Reference treatment
Morphine sulfate solution, 1 mg/mL, was to be infused intravenously by a PCA pump set for 1-mg bolus doses with a lockout period of 5 minutes and a maximum hourly dosage of 10 mg/hr (maximum of 240 doses/24 hours [240 mg/24 hours]).

References

Duration of Treatment: 24 to 72 hours

Prior to the recall of Vioxx® (rofecoxib) on September 30, 2004, all patients were to receive Vioxx® 25 mg 2 to 4 hours prior to surgery and 25 mg each day of the study. After September 30, 2004, the use of NSAIDs or cyclooxygenase Type II (COX-2) inhibitors intraoperatively during the post-operative screening and treatment periods was prohibited.

Population: Fifty-two centers in the US treated a total of 799 patients (395 randomized to IONSYS) for this study.

Key Entry Criteria:

Inclusion criteria:

- post-operative men and women
- 18 years of age and older
- primary unilateral hip replacement
- titrated with IV opioids, and reported their pain was ≤4 on an 11-point scale
- comfortable for at least 30 minutes in the PACU

Exclusion criteria:

- Patients who may be managed with oral opioids, intra-operative spinal anesthesia other than bupivacaine (without epinephrine), intra-operative epidural anesthesia or continuous regional technique; systemic or intra-articular steroids
- Patients who require additional surgical procedures within 72 hours or are scheduled for intensive care;
- Patients who received intra- and/or post-operative administration of opioids other than morphine, hydromorphone, fentanyl, sufentanil or alfentanil.
- Patients with a history of opioid, illicit drug or alcohol use, psychiatric illness, increased intracranial pressure, malignancy
- Pregnancy or nursing

Efficacy assessments:

Primary efficacy variable:

Patient Global Assessments (PGA) of method of pain control at 24 hours

Secondary efficacy variables:

- Pain intensity.
- Ease-of-care assessed by patients, by the physical therapist, floor nurses and research nurses

- The investigator and/or the surgeon were to complete a global assessment of method of pain control after each patient completed participation.
- Adherence of IONSYS and the number of on-demand doses were recorded.
- Information regarding the type and amount of analgesics prescribed for the patient at study completion/termination,
- The date and time of ambulation,
- Eligibility for discharge and actual hospital discharge were recorded.

Safety assessments:

- Oxygen saturation,
- Vital signs (temperature, heart rate, respiratory rate, and blood pressure),
- Topical and systemic adverse events,
- Ramsay sedation scale.
- A physical examination and pregnancy test were also performed during screening. The pregnancy test was required for women of child-bearing potential only if one had not been done 3 days prior to surgery.

Analysis:

- Evaluable for efficacy: included randomized patients who received at least 3 hours of treatment with IONSYS or IV PCA morphine.

- Intent-to-treat (ITT): included randomized patients who received study treatment. This was used in all safety summaries.

Summary Findings:

Efficacy

Primary: The proportion of patients who gave excellent or good ratings for the IONSYS was 83.8% (326/389)

Secondary:

- The frequency of suspected technical failures reported for IONSYS was 5.6% (41/730).

- Of the 730 IONSYS systems used for the ITT population, 90.8% (663/730) of the systems adhered to at least 90.0% of the application site with no edges unattached; 20 systems (2.7%) required taping; and 2 systems (0.3%) fell off.

- Table 10.1.3-2 Summary of Nurse Ease-of-Use Questionnaire (All Nurses Who Provided Care for at Least one or both IONSYS or IV PCA patient)

Subscale	E-TRANS (fentanyl) 40 µg (N=379)	IV PCA morphine (N=325)
Overall Ease-of-Care [b]		
n	305 (80.5%)	294 (90.5%)
Mean (SEM)	0.58 (0.039)	1.16 (0.048)
Median	0.40	1.08
Range	0.0 to 5.0	0.0 to 4.6
Missing	74 (19.5%)	31 (9.5%)
Time-Consuming [c]		
n	309 (81.5%)	298 (91.7%)
Mean (SEM)	0.69 (0.042)	1.24 (0.049)
Median	0.50	1.20
Range	0.0 to 5.0	0.0 to 4.5
Missing	70 (18.5%)	27 (8.3%)
Bothersome [c]		
n	317 (83.6%)	298 (91.7%)
Mean (SEM)	0.44 (0.038)	1.06 (0.050)
Median	0.20	1.00
Range	0.0 to 5.0	0.0 to 4.6
Missing	62 (16.4%)	27 (8.3%)

A lower score suggests that the system was less bothersome and less time consuming to use. Data are abstracted from Table 11.2.7-11A on page 424 of the Sponsor's study report.

Safety

- In the IONSYS group, 305 (77.2%) patients experienced at least one adverse event.
- The most common systemic adverse events in the IONSYS treatment group were nausea and fever.
- Application site reactions (ASRs) (erythema, vesicles, itching, dry and flaky skin, pain and other) were reported as adverse events in 38 (9.6%) IONSYS patients.
- A total of 3 (0.8%) patients in the IONSYS group discontinued from the study because of dyspnea (1) or hypoxia (2).

Reviewer's comment:

This study doe not meet criteria for an adequate and well-controlled clinical trial, but it does provide safety data and additional information about the product when used in a hospital setting. The findings generally support safety of the product for its indicated use in the hospital setting.

10.1.2 Protocol CAPSS-320 Synopsis Of Study Report

Title: Comparison of the Safety and Efficacy of Patient Controlled Analgesia Delivered by Fentanyl HCl Transdermal System Versus Morphine IV Pump for Pain Management after Nonemergent Abdominal or Pelvic Surgery

Objective:
The primary objective of this study was to evaluate the safety and efficacy of IONSYS treatment versus IV PCA morphine for the management of post-operative pain in patients who had undergone non-emergent abdominal or pelvic surgery.

Study Design: multicenter, open-label, randomized, comparative, parallel treatment study.

Study medication, dose schedule, and mode of administration

Test Product
Patients randomized to IONSYS received 40 micrograms (mcg) fentanyl per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 mcg/hour) or a maximum of 80 doses (3.2 mg) with each device.

Reference treatment
Morphine sulfate solution, 1 mg/mL, was to be infused intravenously by a PCA pump set for 1-mg bolus doses with a lockout period of 5 minutes and a maximum hourly dosage of 10 mg/hr (maximum of 240 doses/24 hours [240 mg/24 hours]).

Duration of Treatment: 24 to 72 hours

Population:
Thirty-nine sites in the United States treated 506 patients in this study.

Key Entry Criteria:

Inclusion criteria:

- Patients were post-operative men and women,
- 18 years of age and older who had
- non-emergent abdominal or pelvic surgery,
- titrated to comfort with IV opioids as clinically appropriate,
- reported their pain was ≤4 on an 11-point scale, and stated they were

- comfortable for at least 30 minutes in the PACU.

Exclusion criteria:

- Patients who may be managed with oral opioids, intra-operative spinal anesthesia other than bupivacaine (without epinephrine), intra-operative epidural anesthesia or continuous regional technique, patient controlled epidural analgesia, local anesthetic infiltration of the wound, intraoperative or post-operative NSAIDS, sterioids
- Patients who require additional surgical procedures within 72 hours or are scheduled for intensive care;
- Patients who received intra- and/or post-operative administration of opioids other than morphine, hydromorphone, fentanyl, sufentanil or alfentanil.
- Patients with a history of opioid, illicit or drug or alcohol use, psychiatric illness, increased intracranial pressure, malignancy
- Patients with a history of opioid, illicit or drug or alcohol use, psychiatric illness, increased intracranial pressure, malignancy, inflammatory bowel disease, cardiovascular including bradyarrhythmias, acute or chronic pulmonary disease, sleep apnea, impaired hepatic function, impaired renal function
- Pregnancy or nursing

Efficacy assessments:

Primary efficacy variable:

Patient Global Assessments (PGA) of method of pain control at 24 hours.

Secondary efficacy variables:

- The Patient Ease-of-Care Questionnaire, Pain Management Goal, Nurse Ease-of-Care, Physical Therapist Ease-of-Care Questionnaire,
- Assessment of the Adherence of the IONSYS,
- Non-Routine Events Checklist,
- Post-Study Analgesics,
- Time to Ambulation,
- Time to Discharge, and a
- Brief Pain Inventory

Safety assessments:

- oxygen saturation,
- vital signs (temperature, heart rate, respiratory rate, and blood pressure), topical and systemic adverse events, and the Ramsay Sedation Scale. A
- physical examination and

- pregnancy test were also performed during screening. The pregnancy test was
- required for women of child-bearing potential only if one had not been done 3 days prior to surgery.

Analysis:

- Evaluable for efficacy: included randomized patients who received at least 3 hours of treatment with IONSYS or IV PCA morphine.

- Intent-to-treat (ITT): included randomized patients who received study treatment. This was used in all safety summaries.

Summary Findings:

Efficacy

Primary: The proportion of patients who gave excellent or good ratings for the IONSYS group was 85.6% (214/250).

Secondary:

- The frequency of suspected technical failures reported for IONSYS frequency of suspected technical failures was reported 4.0% (18/453).

- Of the 453 IONSYS used, 94.0% (426/453) of the systems adhered to at least 90.0% of the application site with no edges unattached; 14 systems (3.1%) adhered between 75% to 89%, 2 systems (0.4%) adhered <75% but did not require tape, 7 systems (1.5%) required taping; and 4 systems (0.9%) fell off.

- Table 10.1.3-3 Summary of Nurse Ease-of-Use Questionnaire (All Nurses Who Provided Care for at Least one or both IONSYS or IV PCA patient)

Subscale	E-TRANS (fentanyl) 40 µg (N=232)	IV PCA morphine (N=221)
Overall Ease-of-Care [b]		
n	182 (78.4%)	195 (88.2%)
Mean (SEM)	0.47 (0.037)	1.09 (0.054)
Median	0.32	1.05
Range	0.0 to 2.9	0.0 to 2.9
Missing	50 (21.6%)	26 (11.8%)
Time-Consuming [c]		
n	191 (82.3%)	196 (88.7%)
Mean (SEM)	0.55 (0.041)	1.18 (0.055)
Median	0.40	1.17
Range	0.0 to 2.9	0.0 to 3.0
Missing	41 (17.7%)	25 (11.3%)
Bothersome [c]		
n	186 (80.2%)	196 (88.7%)
Mean (SEM)	0.37 (0.037)	0.99 (0.059)
Median	0.20	0.90
Range	0.0 to 2.9	0.0 to 3.0
Missing	46 (19.8%)	25 (11.3%)

A lower score suggests that the system was less bothersome and less time consuming to use. Data are abstracted from Table 11.2.7-5A on page 352 of the Sponsor's study report.

Safety

- In the IONSYS group, 195 (77%) patients experienced at least one adverse event.
- The most common systemic adverse events in the IONSYS treatment group were nausea and headache.
- Application site reactions (ASRs) (erythema, vesicles, itching, dry and flaky skin, pain and other) were reported as adverse events in 37 (15%) IONSYS patients.
- Three patients (1.2%) in the IONSYS group experienced hypoventilation. No patient in the IONSYS group discontinued from the study because of respiratory system adverse events.

Reviewer's comment:

This study doe not meet criteria for an adequate and well-controlled clinical trial, but it does provide safety data and additional information about the product when used in a hospital setting. The findings generally support safety of the product for its indicated use in the hospital setting.

10.1.3 Protocol FEN-PPA-401 Synopsis Of Study Report

Title: Comparison of Transdermal Fentanyl PCA and IV Morphine PCA in the Management of Post-Operative Pain Control.

Objective:
The primary objective of this study was to evaluate the clinical use of IONSYS® fentanyl treatment and IV morphine PCA treatment for the management of moderate to severe post-operative pain in patients after an elective major abdominal or orthopedic surgical procedure.

Study Design: international, multicenter, randomized, open-label, active comparator, parallel-group study.

Study medication, dose schedule, and mode of administration:

Test Product
Patients randomized to IONSYS received 40 micrograms (mcg) fentanyl per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 mcg/hour) or a maximum of 80 doses (3.2 mg) with each device.

Reference Product
On demand doses with a maximum of 20mg/2hr (240 mg during 24 hours);
IV Patient-Controlled Analgesia (IV morphine PCA).

Duration of Treatment: 24 to 72 hours

Population: This European Union study consisted of a total of 660 treated patients (325 randomized to IONSYS)

Key Entry Criteria:

Inclusion criteria:

- post-operative men and women
- 18 years of age and older
- major elective orthopedic or abdominal surgery
- general or regional anesthesia, not last beyond the operating room period
- titrated with IV opioids, and reported their pain was ≤4 on an 11-point scale
- comfortable for at least 30 minutes in the PACU

Exclusion criteria:

- Patients with a history of opioid, illicit drug or alcohol use, psychiatric illness, respiratory depression because of central nervous system effect, respiratory or renal disease
- Patients who received perioperative administration of opioids other than morphine, alfentanil, fentanyl, sufentanil or remifentanil.
- Other coexisting medical condition associated with severe pain

Efficacy assessments:

Primary efficacy variable:

Patient Global Assessment of Pain at 24 hours

Secondary efficacy variables:

- Pain Intensity
- Patient Global Assessment of Method of Pain Control at 48h, 72h and Last Assessment
- Dropout reason
- On-Demand IONSYS or IV Morphine PCA Doses
- Rescue Medication
- Use of Anti-emetics
- Other Medications
- Suspected Technical Failures of the IONSYSs or IV Morphine PCA Devices
- Assessment of the Adherence of the IONSYS
- Patient Ease-of-Care Questionnaire
- Nurse Ease-of-Care Questionnaire
- Physical Therapist Ease-of-Care Questionnaire

Safety assessments:

- oxygen saturation,
- vital signs (temperature, heart rate, respiratory rate, and blood pressure),
- topical and systemic adverse events,
- clinically significant respiratory depression (rate < 8/minute, upper airway assessment , Glascow Coma Scale assessment)
- physical examination
- pregnancy test were also performed during screening. The pregnancy test was required for women of child-bearing potential only if one had not been done 3 days prior to surgery

Analysis:

- The "evaluable-for-efficacy" population, defined as all randomized patients for whom a PCA device was enabled for at least 3 hours, was used as primary population for the efficacy analysis.

- Randomized patients who received study treatment were used in all safety summaries.

Summary findings:

Efficacy

Primary: The percentages of patients for whom the PGA ratings at 24 hours of the method of pain control were "good" or "excellent" in the evaluable population were 87% (IONSYS) and 88% (IV morphine PCA).

Secondary:

- Suspected device malfunctions or failures were reported in 39 of 325 patients randomized to IONSYS (12.0%) and this number included suspected failures observed prior to application of the system.
- The majority of IONSYS systems adhered to at least 90% of the area with no unattached edges. In 3.2% (n = 24) of systems used, tape was required to secure it.
- Table 10.1.3-1 Summary of Nurse Ease-of-Care Questionnaire at Last Assessment

Subscale Mean (SEM), range	**E-TRANS® fentanyl PCA**	**IV morphine PCA**
Overall Ease of Care (average of time consuming and bothersome subscales)	0.7 (0.04) 0-3	1.2 (0.05) 0-4
Bothersome (items 11-20)	0.6 (0.04) 0-3	1.0 (0.05) 0-4
Time-Consuming (items 1-10)	0.8 (0.04) 0-4	1.4 (0.06) 0-5
Satisfaction (items 21 and 22)	3.8 (0.05) 1-5	3.5 (0.05) 2-5

On the "Bothersome" and "Time-Consuming" subscales, a lower score suggests less bother and less time consumption whereas on the "Satisfaction" subscale, a higher score suggests greater satisfaction. Data are abstracted from sponsors Study Report Table 16, Pg 78

Safety

- In the IONSYS group, 243 of 325 patients (74.8%) experienced at least one adverse event.

- The most common systemic adverse events were nausea and vomiting in the IONSYS treatment group.

- The application site reactions of erythema, itching, and vesicles also occurred commonly at a frequency of 38%, 7%, and 7%, respectively.

- Among all IONSYS patients there were 4 cases (1.2%) of hypoventilation, but none were reported in association with rescue medication.

Reviewer's comment:

This study doe not meet criteria for an adequate and well-controlled clinical trial, but it does provide safety data and additional information about the product when used in a hospital setting. The findings generally support safety of the product for its indicated use in the hospital setting.

34 Page(s) Withheld

- § 552(b)(4) Trade Secret / Confidential
- § 552(b)(5) Deliberative Process
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/s/

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