SYNOPSIS CR013201

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development (J&JPRD)
Name of Finished Product	IONSYS™
Name of Active Ingredient	Fentanyl hydrochloride

Protocol No.: CR013201

Title of Study: A Prospective Safety Surveillance Study of IONSYS™ (Fentanyl HCl)

Study Name: R133119

Coordinating/Principal Investigator: Professor Wappler

Publication (Reference): None:

Study Period: 25 March 2008– 28 September 2008

Phase of Development: Phase 4

Objectives: To document the use of IONSYS™ under routine conditions and obtain a more comprehensive understanding of the safety of the system and complications that may not be spontaneously reported.

Methods: This was a multi-center, non-randomized, non-interventional, comparative, prospective safety surveillance study of postoperative pain management with IONSYS™ (fentanyl HCl). Subjects were screened within 3 weeks prior to surgery or within the time period specified by standard practice for preoperative visits at each study center. Prior to the surgical procedure, informed consent was taken from subjects with planned surgery and anticipated use of opioid pain management for postoperative care. All enrolled subjects received treatment and care according to the standard practices at the study center, including: treatment choice, pain management set-up, and operation. The observation of study subjects began upon admission to the study center for the surgical procedure and continued until discontinuation of IONSYS™ or intravenous (IV) patient controlled analgesia (PCA) opioid treatment. Subjects with ongoing adverse events at termination were followed until all significant changes had resolved or became medically stable. During the period of observation, procedures for recording several key safety measures were provided to increase standardization of measurement and consistency in the documentation of intra-surgical complications, the number of doses of IONSYS™ or IVPCA opioid treatment administered adverse events, and device malfunction.

This was a safety surveillance study of IONSYS™ under conditions of routine clinical care. Prospective assignment of pain management medication was not relevant to study conduct. Intravenous PCA opioid choice was to be determined by the treating physician including the concentration, dose, and lock out period. The subjects were assigned the following treatments during the study:

IONSYS™ (fentanyl HCl 40 µg) system: The IONSYS™ system is a patient-controlled transdermal delivery system designed to provide on-demand delivery of fentanyl through intact skin by user activation of a single output constant current source. Each system contains fentanyl HCl equivalent to 10 mg fentanyl base. A dose of fentanyl was delivered from the system when the user-activated delivery button was depressed twice within 3 seconds. The dose was administered over 10 minutes for a maximum of 6 doses/hour (240 µg/hour) for 24 hours or a maximum of 80 doses (3.2 mg).

Intravenous PCA opioid: IVPCA opioid was selected as the comparator for this study because it is a patient-controlled modality commonly used in clinical practice for postoperative analgesia. The opioids most commonly administered via IVPCA device include, but are not limited to, morphine, fentanyl, and hydromorphone. The choice of opioid concentration, dose, and lockout period was determined by the treating physician.

Number of Subjects (planned and analyzed): Approximately 3,000 subjects treated with IONSYS™ in hospitals were to be enrolled. In addition, a group of approximately 1,500 subjects treated with IVPCA opioid and matched to IONSYS™ subjects were to be enrolled. The study was terminated after 218 subjects were enrolled. A total of 213 enrolled subjects treated with IONSYS™ or IVPCA opioid treatment were included in the safety analysis population.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 years of age or older, who had planned postoperative pain management with IONSYS™ (or IVPCA opioid treatment) were included in the study. Subjects with planned IVPCA opioid treatment who failed to meet the match criteria, or who were having an emergency surgery, were excluded.

Test Product, Dose and Mode of Administration, Batch No.: The IONSYS™ (fentanyl HCl system 40 μg) used in the study was supplied by the study center.

Reference Therapy, Dose and Mode of Administration, Batch No.: The IVPCA opioid solution and the PCA pump used in the study were supplied by the study center.

Duration of Treatment: The duration of treatment with IONSYS™ or IVPCA opioid was as per the standard practices of the participating study center.

Criteria for Evaluation: As this was a safety surveillance study, no efficacy data was collected. Safety was evaluated based on the reported adverse events, laboratory and other tests, vital sign measurements (blood pressures, heart rate, respiratory rate, oxygen saturation and temperature), assessment of Clinically Relevant Respiratory Depression (CRRD), and assessment of intra-surgical complications. No intervals or specific time points were specified for the assessments, as these were performed according to standard practices of the participating study center.

Statistical Methods: Approximately 3,000 subjects treated with IONSYS™ in hospitals were to be evaluated. In addition, a group of approximately 1,500 subjects treated with IV PCA opioid were matched to IONSYS™ subjects with respect to age (within 5 years), gender, body mass index (BMI) (<18.5 versus. 18.5-39.9 versus. >39.9), presurgical status [as per American Society of Anesthesiologists (ASA) score (I-II versus III-V)], surgery risk (high risk versus low risk), hospital type (teaching versus. non-teaching) and site/country. The matching was first attempted within the same center, and extended to subjects in the same country if no match was found. The subjects were matched within a period of 30 days of surgery at the site or 60 days of surgery within the country). With the proposed sample size of 3,000 IONSYS™ treated subjects and 1,500 subjects receiving IVPCA opioids, the study would have 80% power to detect a relative risk of 1.96 (IONSYS™ versus IVPCA opioid), assuming a background rate of 1 event per 100 in the IVPCA opioid comparison group.

Descriptive statistics (mean, standard deviation, median and range) of age, weight, height, and BMI for enrolled subjects by treatment group was provided. Sex, ASA score, surgery risk level (high versus low), and hospital type (teaching versus non-teaching) were summarized as frequency distributions for each treatment group.

Safety Analysis: All enrolled subjects treated with IONSYS™ or IV PCA opioid treatment were included in the safety analysis population. The safety analysis population consisted of all enrolled subjects who received at least one dose of IONSYS™ or IVPCA opioid. Unless otherwise noted, all subjects who received IV PCA opioid were summarized as one treatment group irrespective of the specific opioid. The study was continuously monitored for any safety signals. Descriptive analysis for IONSYS™ treated subjects was performed for the following variables: duration of treatment on IONSYS™, adverse events, total amount of medication delivered from IONSYS™, amount and type of analgesics used concomitantly with IONSYS™, type of analgesics prescribed after treatment with IONSYS™, reason for discontinuation of IONSYS™, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and temperature), and system failure rate. Similar analyses were performed for IVPCA opioid treatment users to facilitate interpretation of event rates observed among IONSYS™ users. Adverse events with onset after the first IONSYS™ or IVPCA opioid treatment application were summarized. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 11.1 and summarized by treatment group, system organ class, preferred term, severity and relationship to study drug.

RESULTS:

This was a multicenter observational study conducted from 25 March 2008 to 28 September 2008 at 17 sites across 4 countries (Austria, Finland, Germany, and Netherlands). Approximately 3,000 subjects treated with IONSYS™ in hospitals were to be enrolled. The study was terminated after 218 subjects were enrolled. Of the 218 enrolled subjects, 203 completed the study treatment. Eight subjects, from the IONSYS™ treatment group were discontinued due to adverse events. A total of 213 subjects treated with IONSYS™ or IVPCA opioid treatment were included in the safety analysis population. One subject from the IONSYS™ treatment group was discontinued due to lack of efficacy.

Of the 213 subjects included in the safety analyses, 123 were females and 90 were males with age ranging from 19 to 85 years and BMI ranging from 18.1 to 46.6 kg/m^2. Six subjects from the IONSYS™ treatment group had a high surgical risk. The majority of the subjects in the IONSYS™ treatment group (86.8%) and all the subjects in the IVPCA treatment group had an ASA score of I to II.

Study Completion/Withdrawal Information
(IONSYS-C-2006-001: All Assessed Subjects Analysis Set)

Status	IONSYS	IVPCA	Total
Term Type	(N=197)	(N=21)	(N=218)
Term Reported	n (%)	n (%)	n (%)
Total no. Subjects With Disposition	197 (100)	21 (100)	218 (100)
IONSYS/IV PCA COMPLETED	186 (94.4)	17 (81.0)	203 (93.1)
WITHDRAWAL/DISCONTINUED	11 (5.6)	4 (19.0)	15 (6.9)
Adverse event	8 (4.1)	0	8 (3.7)
Lack of efficacy	1 (0.5)	0	1 (0.5)
Noncompliance with study drug	0	2 (9.5)	2 (0.9)
Technical problems	1 (0.5)	0	1 (0.5)
Withdrawal of consent	0	1 (4.8)	1 (0.5)
Other	1 (0.5)	1 (4.8)	2 (0.9)
Patient removed IONSYS	1 (0.5)	0	1 (0.5)
Patient didn't need the IV. PCA	0	1 (4.8)	1 (0.5)

Note: Percentages calculated with the number of subjects in each group as denominator.

SAFETY RESULTS:

A total of 71 (33%) subjects experienced at least 1 treatment emergent adverse event (TEAE) during the study. Of these 71 subjects, 67 (34%) from the IONSYS™ treatment group and 4 (25%) subjects from the IVPCA treatment group reported at least 1 TEAE. The most frequently reported adverse events in the IONSYS™ treatment group were general disorders and administration site conditions (35 [16%]), followed by gastrointestinal disorders (26 [13%], skin and subcutaneous tissue disorders (7 [4%]), and cardiac disorders (5 [2%]). Four (25%) subjects from the IVPCA treatment group reported adverse events.

The most commonly reported TEAEs by preferred term were application site erythema, application site vesicles, application site inflammation, nausea, vomiting, flatulence, erythema, bradycardia, and dizziness. The TEAEs such as application site erythema, application site vesicles, application site inflammation were reported only in the IONSYS™ treatment group.

The majority of the adverse events were either mild or moderate in intensity except for myocardial infarction, syncope, femur fracture, and renal failure that were considered to be severe in intensity. The severe adverse events were reported by subjects from the IONSYS™ treatment group.

The majority of the adverse events were considered by the investigator as either probably or possibly related to the study drug administration.

Treatment-Emergent Adverse Events in at Least 2% Subjects by System Organ Class and Preferred Term
(Study IONSYS-C-2006-001: Safety Analysis Set)

System Organ Class Preferred Term	IONSYS (N=197) n (%)	IVPCA (N=16) n (%)
Total no. subjects with adverse events	67 (34)	4 (25)
General disorders and administration site conditions	35 (18)	0
Application site erythema	15 (8)	0
Application site vesicles	13 (7)	0
Application site inflammation	3 (2)	0
Gastrointestinal disorders	26 (13)	3 (19)
Nausea	17 (9)	2 (13)
Vomiting	9 (5)	1 (6)
Flatulence	3 (2)	0
Skin and subcutaneous tissue disorders	7 (4)	0
Erythema	3 (2)	0
Cardiac disorders	5 (3)	0
Bradycardia	3 (2)	0
Nervous system disorders	3 (2)	1 (6)
Dizziness	1 (1)	1 (6)

Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

There was one death reported during the study. One subject from the IONSYS™ treatment group experienced severe myocardial infarction that resulted in death after completion of the study within 72 hours. The investigator considered this event as not related to study drug administration. Six subjects reported serious adverse events (SAEs) during the study, out of which 5 subjects were from the IONSYS™ treatment group. All the SAEs were considered as not related to study drug administration except for 1 SAE of moderate delirium that was considered as possibly related to study drug administration.

Adverse Events Leading to Study Discontinuation

Eight subjects (4%), from the IONSYS™ treatment group, were discontinued from the study due to TEAEs. None of the subjects from the IVPCA treatment group were discontinued due to adverse events. The majority of TEAEs that led to discontinuations were gastrointestinal disorders and nervous system disorders.

Intra-surgical Adverse Events:

Five (3%) subjects from the IONSYS™ treatment group and 2 (13%) subjects from the IVPCA treatment group experienced intrasurgical adverse events. The most commonly reported intrasurgical adverse events were vascular disorders.

Assessment of Clinically Relevant Respiratory Depression

There was no incidence of clinically relevant respiratory depression reported during the study.

Other safety observations

There were no consistent treatment related changes from baseline in the vital signs and physical examination findings during the study.

STUDY LIMITATIONS: This study was terminated after approximately 5% of subjects were enrolled.

CONCLUSION: IONSYS™ was well tolerated when administered under routine conditions for the postoperative pain management. The study was terminated after approximately 5% of subjects were enrolled. Consequently no new conclusions can be drawn from the study compared with previous studies.

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