SYNOPSIS

NAME OF SPONSOR/COMPANY: PriCara, Unit of Ortho-McNeil Inc. **NAME OF FINISHED PRODUCT:** E-TRANS® (fentanyl HCl) system **NAME OF ACTIVE INGREDIENT(S):** Fentanyl HCl	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

Protocol No.: CAPSS-320

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

Principal Investigator: Harold S. Minkowitz, M.D. - Memorial City Hospital, Houston, Texas; US

Publication (Reference): None

Study Initiation/Completion Dates: 18 May 2004 to 11 April 2005	**Phase of development:** IIIb

Objectives: The primary objective of this study was to evaluate the safety and efficacy of E-TRANS®fentanyl treatment versus IV PCA morphine for the management of post-operative pain in patients who had undergone non-emergent abdominal or pelvic surgery. Additional objectives were to assess the safety of the E-TRANS® fentanyl system for pain management in this surgical population and to compare the clinical utility of the E-TRANS® fentanyl system to the IV PCA device.

Methodology: This was a multicenter, open-label, randomized, comparative, parallel treatment study. The study consisted of a screening phase followed by randomization into an open-label treatment phase. The screening phase began up to 21 days prior to surgery and the treatment phase began while the patient was in the post-anesthesia care unit/recovery room (PACU) following surgery. Following surgery, patients were randomized into 1 of 2 treatment groups to receive E-TRANS® fentanyl or IV PCA morphine. The patients randomized to E-TRANS® received fentanyl 40 micrograms (μg) per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 μg/hour) or a maximum of 80 doses (3.2 milligrams [mg]) with each system. Each E-TRANS® fentanyl system would inactivate when 80 doses were used or 24 hours elapsed after the first dose. If necessary, patients received a new system to complete the 24-hour treatment period if 80 doses were used. Otherwise, a new E-TRANS® fentanyl system was applied to a new skin site every 24 hours up to 72 hours. Patients randomized to IV PCA morphine received 1 mg morphine bolus doses with a lockout period of 5 minutes, up to 10 doses/hour (10 mg/hour) to a maximum of 240 doses/24 hours (240 mg/24 hours). Patients were permitted rescue medication as needed (p.r.n.) for re-titration to comfort during the first 3 hours after study medication had been initiated. Patients randomized to E-TRANS® fentanyl were to receive fentanyl IV and patients randomized to IV PCA morphine were to receive IV PCA morphine rescue medication. If administration of the specified rescue medication was not possible, the patient was permitted to receive either morphine or fentanyl. The dosage and frequency was to be in accordance with standard practice at each study site. Patients were permitted to be transitioned to oral analgesics

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Methodology (continued):

at any time after Hour 0 as per the institution's standard practice; however, transition to oral analgesics was not to begin while the patient was still wearing the E-TRANS® fentanyl system or while the IV PCA morphine device was enabled. The treatment phase lasted up to 72 hours. At the end of the 72 hours or upon completion of final study procedures, patients in the E-TRANS® fentanyl group had their last system removed and their analgesic regimen prescribed by their physician. Patients in the IV PCA morphine group completed final study procedures and either continued IV PCA morphine or received another analgesic regimen according to the standard of care at that institution.

Number of Patients (planned and analyzed): The study was planned for 35 centers in the United States. Each center was expected to enroll approximately 12 to 16 patients for a total of approximately 500 treated patients. Of the 42 centers who participated, 39 sites enrolled 506 patients for this study.

Diagnosis and Main Criteria for Inclusion: 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.

Test Product, Dose and Mode of Administration, Batch No.: Patients randomized to E-TRANS® received 40 µg fentanyl per on-demand dose, each delivered over 10 minutes for a maximum of 6 doses/hour (240 µg/hour) or a maximum of 80 doses (3.2 mg) with each system (Batch numbers 0330669 and 0430235).

Reference Therapy, Dose and Mode of Administration, Batch No.: Morphine sulfate solution, 1 mg/mL, infused intravenously by IV PCA pump, set for 1 mg morphine bolus doses with a lockout period of 5 minutes, and a maximum hourly dosage of 10 mg/hr (maximum of 240 doses/24 hours).

Duration of Treatment: The study consists of a screening phase (up to 21 days prior to surgery) followed by randomization into an open-label treatment phase, that lasted up to 72 hours.

Criteria for Evaluation:

Efficacy: Patient Global Assessments (PGA) of method of pain control were completed 24, 48 and 72 hours after treatment was initiated or at study completion/termination. Patients were also assessed periodically during study treatment for pain intensity. Outcome measures related to Ease-of-Care were assessed by patients at 72 hours or at study completion/termination. After all patients completed the study at each individual site, the Nurse Ease-of-Care Questionnaires were completed by floor nurses and research nurses who provided primary care for patients participating in this study. The investigator and/or the surgeon were to complete a global assessment of method of pain control, after each patient completed study participation.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation (continued):

Adherence of the applied E-TRANS® fentanyl systems and the number of on-demand doses administered 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. The reason for discontinuation for each patient who did not complete the study was collected and the proportion of patients who discontinued for insufficient pain relief was tabulated. Data regarding non-routine events (e.g., device malfunction and IV line infiltration) were also collected.

Clinical Use: The Patient Ease-of-Care Questionnaire, Pain Management Goal, Nurse Ease-of-Care Questionnaire, Assessment of Adherence of E-TRANS® fentanyl system, Non-Routine Events Checklist, Post-Study Analgesics, Time to Ambulation, Time to Discharge, and Brief Pain Inventory were also assessed to evaluate clinical use of both treatment groups.

Safety: Safety evaluations included 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 if one had not been done within 3 days prior to surgery.

Statistical Methods: Efficacy parameters were analyzed for both ITT and evaluable for efficacy patients. Two-sided 95% confidence intervals (CI) for treatment difference were constructed to evaluate the equivalence of the 2 treatments for the main efficacy outcomes.

The primary efficacy outcome was success in the PGA of method of pain control at the 24-hour time point in the evaluable for efficacy population (defined as all randomized patients who received at least 3 hours of treatment with E-TRANS® fentanyl or IV PCA morphine). Success was defined as a response of good or excellent on the PGA of method of pain control. For patients who discontinued before 24 hours, the primary efficacy outcome was defined as success at the final PGA obtained at the time of discontinuation.

The statistical objective of the study was to establish that the proportion of successes based on the 24-hour PGA for E-TRANS® fentanyl was equivalent to that for IV PCA morphine. E-TRANS® fentanyl and IV PCA morphine were declared equivalent as methods of pain control if the 2-sided 95% CI for the difference between treatments in the proportion of successes at 24 hours based on the evaluable for efficacy population fell within the interval from -10% to 10%.

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SUMMARY – CONCLUSIONS

EFFICACY, CLINICAL UTILITY, AND EASE-OF-CARE RESULTS:

Efficacy Results:

For the primary efficacy variable:

- Equivalence was demonstrated by similar success (excellent and good) rates for the method of pain control based on the first 24-hour PGA for the E-TRANS® fentanyl group (85.6%) [214/250]) and IV PCA morphine group (84.5% [212/251]); difference=1.1%, 95% CI = -5.1%, 7.4%.

The secondary efficacy variables showed results similar to the primary efficacy variable:

- Among pelvic and abdominal surgery patients, similar rates of success at 24 hours were seen with the PGA in the E-TRANS® fentanyl and IV PCA morphine groups (88.6% vs. 84.7%, respectively, for pelvic surgery patients, and 80.4% vs. 84.0%, respectively, for abdominal surgery patients).
- The E-TRANS® fentanyl group (86.0% [215/250]) had a similar success rate for the last PGA compared with the IV PCA morphine group (84.1% [211/251]); difference=1.9%; 95% CI = -4.3%, 8.2%.
- Results from analysis of the Investigator Global Assessment (IGA) showed E-TRANS® fentanyl was rated higher than IV PCA morphine in method of pain control.
- The proportions of dropouts for any reason was higher in the E-TRANS® fentanyl group (16.0% [40/250]) compared with the IV PCA morphine group (10.8% [27/251]; $P = 0.0847$). There were more dropouts due to inadequate analgesia for the E-TRANS® fentanyl group (8.8% [22/250]) compared with the IV PCA morphine group (2.4% [6/251]) and the difference was statistically significantly, $P = 0.0018$.
- Subgroup analysis showed older (≥ 65 years) patients rated E-TRANS® fentanyl higher than IV PCA morphine as a method of pain control.

Clinical Utility Results:

- The E-TRANS® fentanyl and IV PCA morphine groups had a similar number of IV line problems, time to ambulation, number of steps ambulated, time to eligibility for hospital discharge, time to actual hospital discharge, and disposition at time of discharge.
- The E-TRANS® fentanyl and IV PCA morphine groups had a similar incidence of non-routine events and were transitioned in similar proportion to post-treatment analgesics.
- The E-TRANS® fentanyl system was similar to the IV PCA morphine pump in the number of suspected technical failures.

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS

EFFICACY, CLINICAL UTILITY, AND EASE-OF-CARE RESULTS (continued):

Ease-of-Care Results:

- Patients and nurses rated the E-TRANS® fentanyl system easier to use. Nurses who supervised the use of both the E-TRANS® fentanyl system and IV PCA morphine pump rated E-TRANS® fentanyl system easier to use. Patients and nurses also provided a higher satisfaction rating for the E-TRANS® fentanyl system.

Efficacy Summary:

- The E-TRANS® fentanyl system was equivalent to IV PCA morphine for the management of acute post-operative pain requiring opioids in a medically supervised setting for up to 3 days.
- Results of the analyses for the ITT population were not different in any outcome compared to analyses conducted for the efficacy evaluable population.

SAFETY RESULTS:

- The most common systemic adverse event, in both the E-TRANS® fentanyl and IV PCA morphine groups was nausea. Headache, fever, vomiting, back pain, abdominal pain, application site reactions (ASRs), and dyspepsia were higher (by ≥2.0% of patients) in the E-TRANS® fentanyl group and, pruritus, urinary retention, pharyngitis, tachycardia, anemia, and oliguria were higher (by ≥2.0% of patients) in the IV PCA morphine group.
- Adverse events related to the respiratory system were higher in the IV PCA morphine group (12.2%) compared with the E-TRANS® fentanyl group (7.5%). The most common treatment-emergent respiratory adverse events were pharyngitis and hypoxia. The incidence of hypoxia was 1.6% of patients in the E-TRANS® fentanyl group and 3.1% of patients in the IV PCA morphine group. Treatment-related respiratory events were higher in the IV PCA morphine group (3.9%) as compared to the E-TRANS® fentanyl group (1.6%).
- Adverse events related to the nervous system were higher in the E-TRANS® fentanyl group (11.5%) as compared to the IV PCA morphine group (8.3%). The most frequent treatment-emergent and treatment-related nervous system event was dizziness (5.2%, 4.4% in E-TRANS® fentanyl and 4.3%, 3.9% in IV PCA morphine groups, respectively).
- Adverse events related to the cardiovascular system were similar in both treatment groups (8.3% in E-TRANS® fentanyl and 8.7% in IV PCA morphine). The most frequent treatment-emergent cardiovascular system adverse event was hypertension (2.0% in E-TRANS® fentanyl and 2.4% in IV PCA morphine groups).

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (continued)

SAFETY RESULTS (continued):

- Application Site Reactions :
  - For E-TRANS® fentanyl the following events were reported: edema, erythema, itching, vesicles and other.
  - For IV PCA morphine the following event was reported: IV infusion site reaction.
- Adverse events that were judged to be probably or possibly related or had an unknown relationship to study treatment were recorded in 60.3% of all patients in the E-TRANS® fentanyl group and 55.5% in the IV PCA morphine group.
- Twelve patients in the E-TRANS® fentanyl group and 16 patients in the IV PCA morphine group experienced serious adverse events. Of these 28 patients, 3 patients in the E-TRANS® fentanyl group and 4 patients in the IV PCA morphine group had serious adverse events that were considered related to study medication. One patient, in the IV PCA morphine group, experienced clinically relevant respiratory depression. One patient in the IV PCA morphine group died due to pulmonary embolus, which was not considered treatment-related.
- Thirty-three patients discontinued early due to treatment-emergent adverse events; 14 (42.4%) in the E-TRANS® fentanyl group and 19 (57.6%) in the IV PCA morphine group.
- In evaluating sedation, both the E-TRANS® fentanyl and IV PCA morphine groups scored similarly. The E-TRANS® fentanyl and IV PCA morphine groups were also similar in last and worst assessment of Ramsay Sedation Scale scores.

CONCLUSION:

The E TRANS® fentanyl system was equivalent to IV PCA morphine for the management of acute post-operative pain requiring opioids in a medically supervised setting for up to 3 days in duration. No new safety or tolerability signals were detected during this study.

Date of the report: 12 September 2005

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